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Consideration of the nature of the shock

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A Consideration of
THE NATURE OF SHOCK

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PREFACE

The chief concern of the doctor in the study of disease is the search for an effective method of treatment. The most exact academic knowledge of a disease entity will give us little satisfaction if we are unable to prescribe a remedy which will ameliorate our patient's symptoms and finally cure him.

In order that we may discover an effective treatment for any disease, it is highly desirable that we know the cause and mechanism of the condition. When the cause is once revealed, we at least can intelligently direct our efforts at discovering a method of therapy, if we cannot at once lay hands on an effective remedy. But until the etiology is understood, our efforts cannot advance beyond the stage of empiricism.

It is my intention, therefore, to undertake in this paper a study of the nature of shock, and to see to what extent the causes of this phenomenon, which long defied detection, have been clarified up to the present time.

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SECTION I

DEFINITIONS OF SHOCK

The approach to the study of a given pathological problem is greatly facilitated by an understanding of its characteristic features and of the forms in which it appears, so that we may recognize the subject of our inquiry and know when we are dealing with it. Those who pioneer in a given subject--who work, so to speak, in virgin soil--are denied these advantages; they are the men who must sift out the pertinent facts and clarify the problem to the point where it can be clearly defined.

Because the passion for a clear understanding is a continuous spur to the scientific mind, many an early worker sought to express in a definition the results of his investigations in the field of shock. Those who followed formulated new definitions, based upon their own contributions and upon the work of their predecessors. Thus we have a long series of definitions of shock, ever changing, each representing the current knowledge of the subject at the time it was proposed. A consideration of a few of these is of interest, as it will introduce the reader to the essential features of shock and will serve to show the evolution which our conceptions of shock have undergone since its study was begun.

The ideas of the nature of shock which were popular among the early investigators of the subject were based upon observations of the effect of severe injuries, and were rather vague. We find references to "loss of nervous fluid", "a species of functional concussion", and "shock to the nervous system"--the last representing the original implication of the term "shock", and the one which is retained by the laity to the present day. This usage persisted even in medicine into the latter half of the nineteenth century; Fischer stated in 1870 that "Shock is produced simply by the concussion of the part, independent of pain or loss of blood" (83,c).

The pathological changes of shock defied detection until after the War; as late as 1914 Mann wrote that "No lesions of any organ or organs the presence of which will account for all the phenomena of shock have ever been conclusively demonstrated" (43). Even the physiological features were but imperfectly understood, and most of the older clinicians, while recognizing the fact that a diminished volume of circulating blood is the cardinal characteristic of shock, attributed this decrease to various forms of vasomotor inactivity (28). Hence the earliest definitions which can still be considered acceptable are those based on the clinical picture of shock; Mann, Meltzer, Porter and others emphasized this fact before the

War (43). Cannon, after quoting accounts of typical cases, says that "From the symptoms appearing in such cases as these, therefore, we may say that shock is a general bodily state which occurs after severe injury and which is characterized by...." and goes on to enumerate the chief clinical features of shock, as described in Section II of this paper (11).

During the War, of course, attention was focused largely upon the shock which resulted from extensive wounds. As a result of the knowledge thus gained, the post-war years brought recognition of the fact that shock was a condition common to grave bodily insults of many kinds, seen not only after wounds but also following severe hemorrhage, burns, abdominal emergencies, acute infections, and in moribund states from various causes. Evidence of this widened viewpoint is seen in the definition of Cope, in 1928: "The term shock signifies a condition following the application of harmful stimuli (traumatic or toxic) or the depletion of the body fluids, in which there is clinically demonstrable depression of the vital processes of the body, particularly the circulation and metabolism" (81,b).

It was soon established beyond a doubt, however, that certain physiological changes which during the War were proved to be characteristic of wound shock were also

constant factors in shock originating from the other causes which I have just described. Here we have a group of physiological features which are now universally accepted, and which Moon says "may be formulated into a useful definition of the condition: 'Shock is a circulatory deficiency, neither cardiac nor vasomotor in origin, characterized by decreased blood volume, decreased cardiac output (reduced volume flow) and by increased concentration of the blood'"(48).

Before concluding this section, I should say that two types of shock have long been recognized: namely, primary or immediate shock and secondary or delayed shock. The primary form may be transient and apparently identical to fainting or syncope; or it may be severe and prolonged. In the latter case, the problem is the same as that of established secondary shock. The type of shock which is of chief significance, from the standpoint both of its much greater frequency and of the number of fatalities it causes, is secondary or delayed shock; it is this type which will be considered in the following sections except where specific reference is made to the primary form.

SECTION II

THE CLINICAL PICTURE OF SHOCK

In order to give the reader a vivid first impression of the clinical picture of established shock, I cannot do better than to repeat a case description which was given by Fischer, one of the pioneers in the study of shock, in 1870:

> The patient, a strong and perfectly healthy young man, was struck in the abdomen by the pole of a carriage drawn by runaway horsee. The grave symptoms and the alarming look which he still presents made their appearance immediately after the accident. He lies perfectly quiet and pays no attention whatever to events about him. The pupils are dilated and react slowly to light. He stares purposelessly and apathetically straight before him. His skin and such parts of the mucous membranes as are visible are as pale as marble, and his hands and lips have a bluish tinge. Large drops of sweat hang on his forehead and eyebrows, his whole body feels cold to the hand, and a thermometer indicates a degree and a half below the normal in the axilla. Sensibility is much blunted over the whole body, and only when a very painful impression is made on the patient does he fretfully pull a wry face and make a languid defensive movement. If the limbs are lifted and then let go, they immediately fall as if dead. The pulse is almost imperceptible and very rapid. The arteries are small and the tension very low. The patient is conscious, but replies slowly and only when repeatedly and importunely questioned. On being thus questioned, he complains of cold, faintness, and deadness of the extremities. His respiration is characterized by long, deep, sighing inspirations, alternating with very superficial ones. While being brought to the hospital he vomitied several times (83,a).

This remarkable account includes nearly all of the clinical features of shock which we recognize today. They are, without exception, the result of such a marked impair-

ment of the circulation that the tissues and organs of the body suffer from lack of blood: for, as we have already seen, a decrease in the quantity of circulating blood is a constant characteristic of shock.

The weak and rapid pulse, the low blood pressure, the pallor and cyanosis, and the cold extremities are the direct result of an insufficiency of blood supply to the peripheral parts. The rapid heart rate represents an attempt to compensate for the lowered volume of blood. The other features described are the manifestations of a lowered metabolism incident to deficient oxygen supply.

Profuse perspiration is a characteristic of severe shock. This factor adds to the diminution of the body fluids, and creates an insatiable thirst which represents the demand of the body for their replacement. However, the vomiting which almost invariably follows the administration of water by mouth prevents its assimilation. These features, and the low blood volume even when there has been no hemorrhage, indicate that the metabolism of fluids is greatly altered in shock.

The mental state of the shocked patient appears to vary somewhat in different cases, but there is general agreement that consciousness is seldom entirely lost. The patient may quickly lapse into an apathetic state, indifferent to his surroundings and slow to respond to ques-

tions (28,11). Or he may be extremely alert, and reply sensibly, if slowly, to any questions asked him (28,37). Keith found that most of the cases he observed showed marked restlessness, often being difficult to control (37). The insensibility to pain stimuli and to the pain of their wounds is very common in shocked patients.

This, then, is the picture of established shock; and it is the same whether the shock is the severe type of primary shock or the more common secondary form. However, as Stanbro points out, it is not the picture we should look for but the one we should attempt to prevent or abort. When the shock has become well established, he says, treatment is of no avail, and no known agent will bring the blood flow back to normal (67). Concerning this statement there is almost universal accord; McNee and his co-workers, for example, concluded that "Cases exhibiting the severer degrees of shock die in spite of all the methods of treatment at our disposal" (46).

It is evident, then, that we must look for shock in its incipiency if we are to give the patient any benefit from our treatment. The signs and symptoms of early shock, however, are not distinctive. Keith, describing mild states of shock in patients whom he calls "compensated cases", observed that the general condition was good; the patient had no distressing symptoms except the local pain

of the wound and a feeling of general weakness. He was often very pale, but the blood pressure remained above 100 mm of mercury and the pulse, while increased to 90 or 100, remained of good quality (37). And even in a patient exhibiting only these mild symptoms, the blood volume may have been diminished by at least half the amount necessary to produce a severe state of shock.

We shall see later that the early diagnosis of shock cannot be made on a basis of symptoms and signs, but depends on laboratory detection of the blood concentration which accompanies the decrease in volume of circulating fluid.

SECTION III

EARLY CONCEPTIONS OF SHOCK

With the exception of certain simple procedures such as circumcisions and operations on the extremities, the treatment of wounds constituted the major part of surgery until late in the nineteenth century. The information which has been gained, and continues to accumulate, from the study of wounds has contributed immeasurably to every branch of surgery. Hippocrates, who said that war is the only proper school for the surgeon, did not describe shock but recognized important principles concerning the prognosis in the wounded. He stated that "Wounds are very dangerous when there is some large nerve, vein, or artery injured, for the convulsion and the flow of escaping venal or arterial blood prostrates the wounded one and exhausts his strength" (6).

In very early times it was observed that patients who had been injured sometimes fell into a depressed lethargic state in which death might occur. Autopsies in such cases not infrequently revealed no lesion adequate to account for death (Mann, 43).

The picture of shock was recognized as a clinical entity early in the 18th century, in the effect of wounds and trauma such as occurred in gunshot injuries. Le Dran,

in 1737, said that "Such wounds require the surgeon's greatest attention....It is scarcely possible that a solid body, driven by gunpowder, should strike any part without communicating at the same time an agitation proportionable....This agitation is technically termed 'commotion', and we learn from daily experience that it is often communicated to the whole machine, whereby the nervous system is galled and irritated....Thus some wounded experience torpor and dullness; others have repeated faintings: some have convulsive movements, as hiccup, vomiting; some become leaden colored" (87).

According to Groeningen, James Latta in 1795 was the first to employ the term "shock" with the meaning that is now attached to it: that is, with reference to the symptom complex produced rather than to the "concussion" or nervous insult which was supposed to cause the picture (28).

Shock was usually discussed by the earlier writers under the title of "inflammation" or "irritation". John Hunter considered the amputation of extremities of soldiers injured at was inadvisable since the operation was a violence added to the injury. He stated that in the case of the injury alone the patient suffered only from the "inflammation", while amputation added the insults of loss of substance and loss of more blood; "as it is to be supposed that a great deal has been lost from the accident,

not to mention the awkward manner in which it must have been done". Yet even with these views on the subject, Hunter yielded to the prevailing opinion of his time and advised blood-letting, saying that "it makes the circulation more free, so that the heart labors less" (85).

Sir Astley Cooper, a pupil of Hunter, retains something of the latter's conception of "inflammation", but he also shows a clear recognition of the clinical picture now known as shock. Cooper writes that the most severe method by which fatal injuries cause death is by shock to the nervous system, and gives as an illustration the case of a man who was severely burned and who when seen had a small feeble pulse and cold skin, and died in eight hours (6).

Ambroise Paré described, under the title of "Syncope and Heart Failure", what is known today as primary shock or collapse (1840). In his own words, "Syncope is a sudden and strong failure of the faculties and senses, and principally of the vitality, and the sick one remains without any movement....The signs of syncope are when the ill one pales, and when there comes to him a slight sweat, cessation of the movements of the arteries, whereupon soon afterwards he falls to the ground, without any feeling and movement, and becomes seemingly cold throughout, in such fashion that he resembles more a dead man than a live one. Many who fall in syncope, if they are not succorred, die" (90).

Mann points out that although the ideas of the older writers on shock were vague, they foreshadowed nearly all the modern theories of this condition. "Thus Travers (1826) states that 'shock is a species of functional concussion by which the influence of the brain over the organ of circulation is deranged or suspended'. And Savoy (1860) writes that 'death from shock results from sudden and violent impressions in some portions of the nervous system acting upon the heart and destroying its action'. Thus writers have anticipated the modern (1914) theories of vaso-motor paralysis and cardiac failure". And Meltzer's inhibition theory is suggested by the definition of Delcasse (1834), in which shock is said to be "an arrest of innervation without which all organs pass into insensibility" (43).

Travers, says Blalock, was far in advance of his time in his ideas concerning shock, particularly as regards treatment. He did not agree with his contemporaries on the value of blood-letting, saying, "The custom of letting blood indiscriminately after injuries is so irrational, that the authority of long established customs forms no excuse for it. I have seen a practitioner tie up the arm of a person to bleed him after a fall, in a pale cold stun, in which the pulse could scarcely be felt at the wrist"(94).

Near the end of the nineteenth century, there appeared

several opinions to the effect that shock resulted from cardiac failure. Jordan said (1867) that "Shock may be defined in general terms as a peculiar condition of the animal system characterized by a depression of all its functions, the result of a powerful impression applied to the nervous centers, or to a portion of the peripheral nervous expansion....Every cause, the operation of which gives rise to shock, whether through the intervention of the nervous system or not, acts upon the central organ of circulation and diminishes its force. With unimpaired cardiac action, shock is impossible" (36).

Vale reports that surgeons paid little attention to shock in the first half of the nineteenth century. "Nor is this strange", he adds, "when we remember what elementary problems, as they appear today, engaged attention. They had not an inkling of the healing of an amputated wound by first intention, almost as many weeks as now days being required for its treatment. Primary and secondary hemorrhage were dangers but imperfectly combatted. 'The few who survived the bleeding lingered through all the miseries of a nine months' cure, tedious and imperfect, with a conical, ulcerated and tender stump' (John Bell, 1795)" (70).

The most significant of the early experimental work appeared in 1863, in the well-known "Klopfersuch" of Goltz.

This investigator found that repeated slight blows on the viscera of a suspended frog caused reflex inhibition of the heart through the vagus and a lessening of vascular tone generally throughout the body and especially in the abdominal cavity. Goltz produced by this method what is known as "primary shock" or "collapse", and little has been added to our knowledge concerning the condition since his results were reported. The explanation which he gave, Blalock says, seems to be entirely satisfactory (84)(cf.p.78).

The first well-defined theory of the etiology of shock, based on the work of Goltz, was proposed by Fischer in 1870, although a similar view had been suggested by Mitchell and co-workers six years earlier. Fischer assumed that traumatic shock consists of a vasomotor paralysis, especially in the splanchnic area, where the bulk of the blood is accumulated, with a consequent anemia in other parts. Shock, then was a hemorrhage into the body's own large veins. Fischer believed the vascular disturbance to be the primary cause, and all other symptoms were secondary to the resulting anemia of the peripheral parts (83,b).

This hypothesis of Fischer was only one of many theories of traumatic shock based on damage to the vasomotor apparatus, which were held by almost all the older clinicians. The conception was that in various ways, according

to the particular theory, the tone of the vasomotor mechanism is depressed with resultant relaxation of the peripheral blood vessels: in consequence, the capacity of the vessels is so greatly increased that little blood is returned to the heart (28). Mitchell and Keen believed that a reflex paralysis of the vasomotor center occurred; their studies (1864) were based in part upon the work of Claude Bernard on the sympathetic control of vasomotor tone. Porter ascribed shock to fat emboli in the vasomotor region, after having produced shock in animals by injecting fats into the vertebral arteries (91).

These theories accounted very well for the clinical features of shock, such as the low arterial pressure, the collapsed peripheral veins, and the cold skin. They also explain the similarity between the clinical pictures of shock and hemorrhage: in the former the loss of blood, according to the hypothesis of vasomotor inactivity, is into the capacious splanchnic vessels; in the latter, to the exterior.

Without doubt the best known of the theories that shock was due to inactivity of the vasomotor center, however, was that of Crile. His interpretation of his extensive experimental work, which appeared in 1897, was that shock is caused primarily by excessive stimulation of afferent nerves by physical trauma, pain, fear, and infec-

tion. These stimuli finally lead to exhaustion of the vasomotor center; when this breakdown occurs, the arteries lose their tone, and the resulting low blood pressure permits the blood to accumulate in the great vessels. As a result, the output of the heart fails because of lack of filling during diastole (20).

The basis for these views was the results which Crile was able to obtain through stimulation of afferent nerves by cutting, tearing or burning the skin and the sensory nerve trunks. These "strong irritations caused, as a rule, a more or less strong rise of blood pressure during the stimulation". Repeated stimulation of the skin or nerve trunks leads at first to a diminution of the rise produced, then to a stage in which stimulation has no effect on the blood pressure. At this stage the pressure is very low and cannot be permanently improved by any form of treatment. This, according to Crile, is the stage of surgical shock. The development of shock is hastened by the strength of the stimuli and by the amount of tissue involved in the stimulation; under all circumstances, however, its development is always a slow and gradual one.

Failure of the vasomotor center, therefore, was thought by Crile to be the essential cause of shock, and the consequent fall in blood pressure accounts for the other symptoms. In this his beliefs were comparable to

those of Fischer (p.14), who differed only in that he gave no definite cause for the vasomotor relaxation.

The views of Crile were widely accepted in the surgical world and were endorsed by such prominent men as Victor Horsely and Harvey Cushing (47), but they did not hold the field uncontested for long. In 1905, Malcolm submitted the theory that the arteries are tensely and actively contracted in shock (42). Injury to a nerve, he states, causes a contraction of the arterioles throughout the body; if severe enough, this extends to the larger vessels. Thus the radial arteries may be so small that they cannot be felt. The splanchnic vessels are probably larger than those of the rest of the body (is this a concession to the weight of popular opinion?), but there is no loss of tone; if there were loss of tone in the splanchnic vessels, the patient would die, as from hemorrhage. The constriction subjects the blood to pressure, thus forcing the plasma into the tissues and raising the concentration of the blood. Death is due to, or at least accompanied by, exclusion of blood from the tissues supplied by the systemic circulation (42).

Cannon says that the basis for this statement appears to have been the clinical observation that the more profound the degree of shock, the paler are the tissues; pallor of the peritoneum, for example, is noted early in

shock. Recognition of the very important concepts of diminished blood volume and increased concentration was drawn from the marked benefits which resulted when the blood volume was increased by transfusions. In 1909, according to Cannon (11), Malcolm says that the reduction of blood volume may decrease the blood pressure "until the vasomotor and other nerve centers are starved, and life cannot be maintained".

In 1907 Boise expressed the belief that shock was accompanied by vasoconstriction. "I shall endeavor to demonstrate in this paper," he wrote, "that the essential cause of shock is excessive sympathetic irritation, manifested mainly by a tonic contration of the heart and arterioles". From the fact that in animals dead of shock the great veins and venae cavae were much dilated and the heart contracted and empty (according to Crile's experiments, which Boise seems to have accepted but differently interpreted) he thinks that death is due to spasmodic or exaggerated contraction of the heart, with deficient diastole which prevents its filling (7).

Boise also pointed out that vasomotor exhaustion alone, even if this phenomenon did occur, is not sufficient to account for shock, since complete destruction of this center gives a drop in blood pressure only to about 50 mm of mercury, whereas in shock there is often as low a pres-

sure as 20 mm. And Seelig and Lyon reported that a rise of blood pressure was obtained in all stages of shock by stimulation of the central end of the vagus, indicating that the vasomotor center is active.(63) These are some of the first signs of a great deal of experimental evidence against the theory of vasomotor exhaustion.

Howell (1903) favored the hypothesis of inhibition as a cause of shock. Dividing shock into two forms, cardiac and vascular, he ascribed the rapid heart rate of the former to inhibition of the vagus center in the medulla and the latter to inhibition of the vasomotor center (34). "A consideration of the various records obtained in these experiments", he says, "shows that the two most striking symptoms of shock, namely the rapid feeble heart rate and the paralysis of the vasoconstrictor center, may occur independently of each other to a certain extent and justify the distinction sometimes between cardiac shock and vascular shock. In cardiac shock the result is practically the same as that obtained by the section of both vagi with the exception that the heart beats are usually more feeble. We may assume that in cardiac shock the most important factor is a partial or total suspension of activity of the cardio-inhibitory center....By vascular shock is meant a more or less complete loss of arterial tone, which expresses itself in a correspondingly long continued drop

of the general blood pressure." Howell believed that the strong inhibition of these centers led to long-continued suspension of activity, partial or complete, and in this way caused shock.

Meltzer submitted in 1908 the theory of functional inhibition of all the organs of the body. "On the basis of these considerations", he stated, "I venture the assumption, which is not new, that the various injuries which are capable of bringing on shock, do so by favoring the development of the inhibitory side of all the functions of the body. This predominance of inhibition makes its appearance at first in those functions which are of less immediate importance to life, and are, therefore, less insured by safeguards protecting their equilibrium. With increased injury the inhibition spreads also to the more vital and, therefore, better protected functions of the nervous system" (47).

The theory of "acapnia" as a cause of shock was first formulated by Henderson in 1908, and has been developed by him since then in an extensive series of papers. He claims that such factors as pain, fear, or the administration of ether will induce excessive respiration, and this in turn will lead to a lowering of the carbon dioxide content of the blood. The result of this acapnia is a failure of what Henderson calls the "veno-pressor mechanism",

consisting of the tonus of the tissues and the osmotic processes, which maintains the blood pressure. The effect of acapnia on this system is a diminution of the tone of the contractile tissues, which normally prevents venous stasis by compressing the capillaries, and an upsetting of the normal balance of osmotic forces so as to induce a passage of water out of the blood into the tissues. Thus a low venous pressure is produced. Acapnia also increases the tone of the heart muscle, providing an additional impediment to the filling of the heart in the face of the low venous pressure (32).

To summarize, the sequence which Henderson gives is as follows: (a) hyperpnea; (b) acapnia; (c) failure of the veno-pressor mechanism; (d) venous anoxemia, tissue asphyxia and acidosis; and (e) acute oligemia.

In concluding this résumé, I may say that I have made no attempt to include the names of all of the investigators of the phenomenon of shock during the pre-war period, or even the major part of them. My aim has been simply to give some idea of the early conceptions of shock and also a brief outline of the chief theories which came into prominence up to this time, with mention of some of the best known exponents of these theories. I have not considered the experimental work of other men who, while offering no

new suggestions as to the actual cause of shock, nevertheless made substantial contributions to our understanding of its pathology. Some of these workers will be mentioned later in this paper. Further attention will also be given to the theories which I have introduced in this section, and we shall see how they stood the tests of time and critical investigation.

SECTION IV

CONTRIBUTIONS DURING THE WAR PERIOD

Observations Made Early in the War

The onset of the World War, coming as it did at a time when the prevailing conceptions of shock were in a very unsettled state, provided practically unlimited opportunity for the study of this subject. It is not surprising, therefore, that during this period our knowledge of shock increased tremendously, and the theory of its cause which is given most credence today had its inception.

E. W. Archibald, a military surgeon who spent four months in the casualty clearing stations, or hospitals close behind the front line in France, reported that "In the casualty clearing stations shock is seen to an extent unparalleled in the experience of any surgeon at home. The very frequency of it, and the terrible nature of it, were impressive, and, not less so, our inability to rescue such patients when the degree of shock was really serious" (1).

The association between shock and certain factors such as hemorrhage, pain, cold, mental distress and rough handling soon became evident. The rôle played by hemorrhage in particular was seen to be very large, and the difficulty in distinguishing the effects of hemorrhage

alone from those of shock was soon recognized (72). Laboratory evidence corroborated these clinical observations; Mann writes, in 1915, that his experiments "seem to prove that the reason for the common symptoms of shock and hemorrhage is that they have a common pathology", and goes on to say that the clinical signs of shock are due to a loss of circulatory fluid: "In shock a large percentage of the blood is as effectually lost as if shed" (44). Thus we see that the concept of a diminished blood volume appeared early, though proof of this factor of shock was delayed until shortly before the end of the war.

It was also noted that if a patient in shock, or even showing a tendency to shock, underwent surgery, the operation often turned the balance against him. Even after pre-operative treatment of shock had apparently made the patient a moderately good risk, surgery was often followed by a fatal outcome. In many of these cases the immediate post-operative condition appeared to be so good as to warrant a favorable prognosis, yet the patient gradually developed the clinical picture of shock and died in spite of all that was done for him (Wallace,72).

The pooling of blood in the visceral vessels remained, however, the most popular explanation of the phenomenon of shock, although as we have seen (pp.17-18), dissenting voices had begun to make themselves heard. In 1913 Risley

reported experiments which led him to believe that a local accumulation of blood in the splanchnic area was the cause of shock. "There is sufficient evidence at hand", he says, "to establish at least a high degree of probability that shock in operations on the splanchnic area is largely caused by disturbance of the local splanchnic vasomotor mechanism. Exposure of the peritoneum to the air and drying gives splanchnic vasodilatation" (55). Mann agreed that there was a local accumulation of blood in the viscera and said that its cause was the same as that of inflammation in any other irritated area; the gravity of its import in the splanchnic area was imputed to the great vaacularity of this region (44). However, shock was produced in most of these experiments by traumatizing the intestines, and it was proved at a later date that this method gives more visceral congestion than is seen in shock produced in other ways.

It is not quite clear whether the accumulation of blood referred to by Risley and Mann was in the minute vessels or in the large veins of the abdomen. Whichever they meant, the idea of dilatation and engorgement of the great veins, so predominant in the past, was soon subjected to serious doubt as a result of the large number of laparotomies done on soldiers in shock. Wallace and his associates said that although it was commonly stated

and apparently accepted by many that traumatic shock is due to accumulation of blood in the splanchnic area, "in the course of many hundreds of surgical operations on patients in all degrees of shock, we found no primary splanchnic congestion to exist....we see no ground for the assertion that a primary dilatation of the blood vessels in the splanchnic area occurs" (73). This evidence supported the conception of oligemia, but was against the hypothesis of lessened activity of the vasomotor center.

The situation remained about the same, with surgeons still directing their efforts toward curing shock, rather than preventing it, until 1917, when an investigation disclosed that the wounded soldier possessed considerable recuperative powers in the early stages of shock. This was evidenced by the fact that during transit a turn for the worse, with a drop in blood pressure, could be remedied several times by simply giving the patient rest, warmth, and fluids. It was evidently of great importance, therefore, to minimize the time during which the patient was subjected to the detrimental effects of transportation and delayed treatment; that is, the time during which the "shock-producing factors" of trauma, cold, pain, fear, exhaustion, etc., remained active. That these are very real factors may be realized by the description of the journey of a wounded soldier from the front lines to the

dressing station: though frequently in a state of fatigue, cold and wet even before he is injured, the soldier must be jolted along on a stretcher for some thousand yards of communication trench, not infrequently under fire, then carried a mile or so in a horse ambulance over roads pitted with shell holes, then transferred to a motor ambulance and given another rough ride; add to this a couple of changes of dressing of a painful wound, a certain loss of blood even with the best of care, and finally the continued effect of cold, and it is evident that we have a very favorable set of circumstances for the production of shock (Archibald,1).

Realization of these facts led to pushing measures of treatment toward the front line and giving warmth, rest, fluids and better splints at once. If shock developed in spite of these measures, it was treated as soon as arrangements could possibly be made. Good results were evident at once when these measures were instituted.

At about this time it was clearly established that shock was of two varieties: primary and secondary. The primary type was not often seen; Santy, a French surgeon who had much experience in the aid stations near the front, said that apart from those who die on the field, the occurrence of shock in the wounded soldier when seen soon after the infliction of his injury is extremely rare. The loss

of even a strictly moderate amount of blood, however, together with the distresses of transport, will frequently result in the appearance of secondary shock before his arrival at the hospital (93). It was recognized that although primary shock is usually temporary, it sometimes persists and passes into the secondary type. The latter, which usually appears several hours after the injury, or not until the next day, is by far the most important from the standpoint of the number of fatalities it causes.

The recognition of the late onset of secondary shock was important. It did not refute the hypothesis of vasomotor inactivity, but it did open the way for the theory of traumatic toxemia, since this theory required time for the elaboration of the toxin. Although irritation from a badly splinted thigh might give vasomotor exhaustion, it might also cause the formation of a toxic product from continued damage to muscles; and this toxin could conceivably give rise to changes in function which would produce the picture of shock (Wallace,72).

The accumulation of new evidence concerning the problem of shock which I have described up to this point resulted from the efforts of a number of different investigators, working for the most part independently of one another. One is not surprised, therefore, at the fragmentary nature of these contributions. However, most of

them are suggestive of future promise, and a few are the expression of principles which were destined to become firmly established.

The Blood Pressure in Primary and Secondary Shock

In the middle stages of the War, when the relatively stable condition of the fighting lines made possible a more careful study of shock in the wounded arriving in advanced hospital units, a better correlation of laboratory and clinical observations was attempted. In August, 1917, the Medical Research Committee of Great Britain formed a special investigation committee to undertake the coordination of inquiries into surgical shock and allied conditions. This "shock committee" did much to bring about a settled condition in the state of information concerning the subject of its investigations (35).

In order to obtain more information regarding the development of shock, arrangements were made to record continuous histories of wounded men from the time of their injuries until shock appeared. As a result of this procedure the distinction between primary and secondary shock was clarified. Fraser and Cowell reported that blood pressure readings taken in the line on various types of wounds at very short intervals after their infliction, showed two very distinct groups:

(1) The hypertension group, in which the systolic pressure varies from 150 to 160 or even more.

(2) The hypotension group, in which the pressure varies from 90 down to 40 mm.

Practically no cases showed an intermediate or normal blood pressure (29).

The blood pressure of the patients in group (1), after rest in bed and in the absence of the "shock-producing factors" described previously, gradually fell to normal levels and remained there. These were the patients whose wounds and subsequent experience were not sufficient to produce shock. Patients in the hypotension group, on the other hand, are pale, clammy and pulseless when they are first seen, and the earliest blood pressures which may be made are found to be low; in other words, these men are in a state of more or less profound shock soon after they receive their injuries. This is the condition to which the name primary shock was given. This type of shock is occasionally seen in moderately severe wounds in which one would not expect such a marked physiological reaction; but its most frequent occurrence is in serious wounds which are inevitably mortal, or which will cause death unless the patient can be given surgical attention within a short time. Primary shock appears to be more likely to occur in men of emotional instability who have nervous or "high-

strung" temperaments, and in these men it may accompany comparatively trivial wounds (29,18).

Primary shock may be rapidly progressive and lead to death within an hour. Other cases may be kept from progressing and later recover; some of these seem to do surprisingly well. However, either a patient in primary shock or an injured man who shows no signs of shock--that is, a man who is in the hypertension group when first seen--is very likely to gradually pass into what is known as secondary shock because of its delayed onset, if he is subjected to the detrimental "shock-producing factors" of pain, cold, wet, transportation and hemorrhage. These factors are, to a considerable degree, controllable, so secondary shock is usually a result of lack of proper care. Like the primary variety, this type may either improve or grow worse according to the treatment given and the severity of the wounds. The secondary type of shock is seen with much greater frequency than the primary.

The accompanying charts by Cowell (19) show graphically the more common changes in blood pressure which are seen in shock of the two types, and the various kinds of outcome that may be expected.

The Blood Pressure as a Criterion of Shock. It soon became evident, however, that the blood pressure alone was not dependable as a criterion of the degree of shock

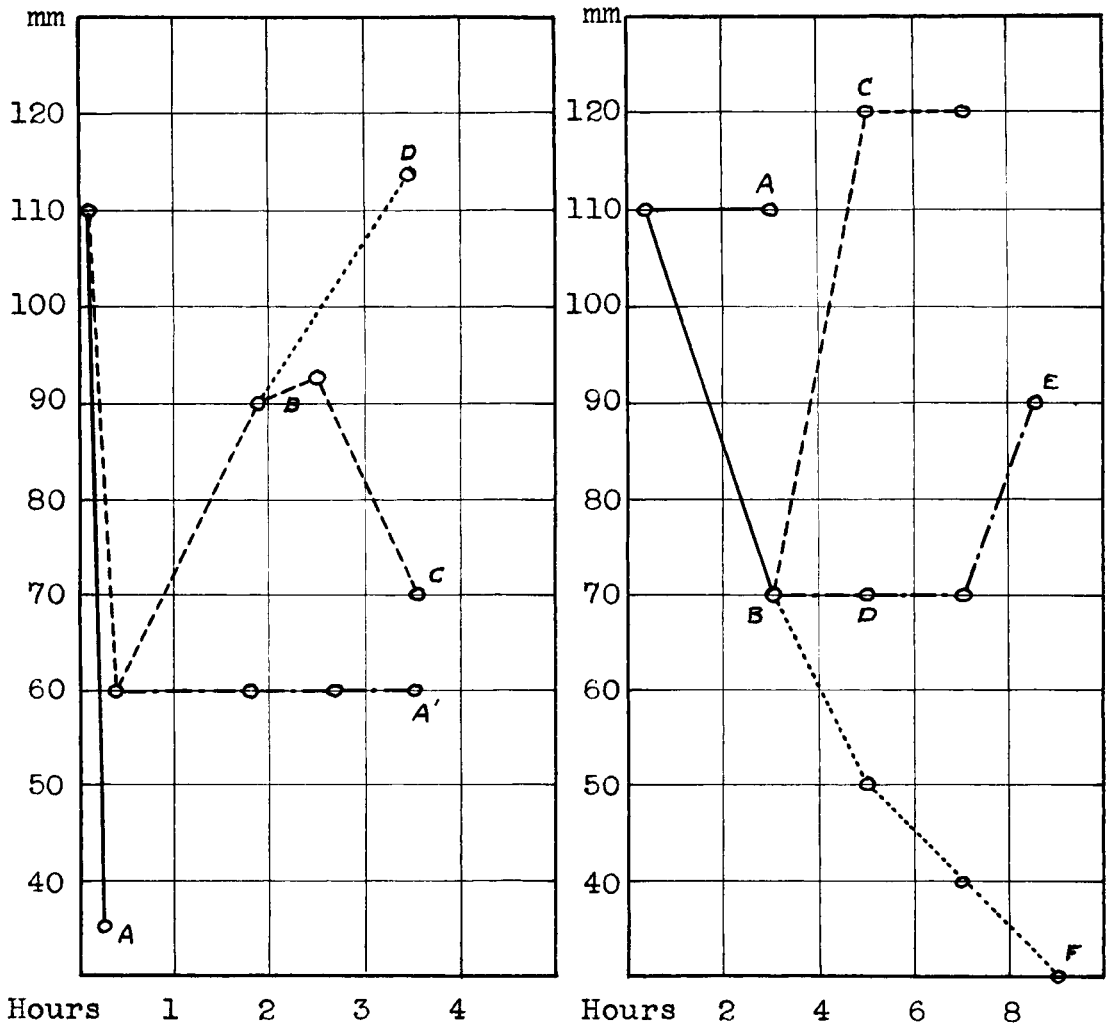

Fig. 1. Primary wound shock curves (diagramatic). Following a severe anatomical injury, instant wound shock may develop, which may be fatal in a shorter or longer time, as shown at A or A'. Under favorable circumstances, the pressure may rise to B, but drop later to C. At this point the primary shock has merged into the secondary wound shock.
[I have added line B-D to show that many cases of primary wound shock permanently recover.]

Fig. 2. Secondary wound shock curves (diagramatic). In many of the cases of moderately severe wounds the pressure will remain level at A. In others it falls with the establishment of secondary wound shock, B. At this point the patient may react quickly to treatment, C, or after more prolonged treatment at D, to E. In the absence of favorable circumstances, the pressure goes steadily down, and the case terminates fatally in from 12 to 14 hours.
(Cowell,19)

or even of the presence or absence of shock, unless it was markedly lowered. It was found that there might be a considerable reduction of the total blood volume without any appreciable drop in blood pressure. Robertson and Bock stated that "This is due undoubtedly to the well-recognized fact that the vasomotor mechanism responds within certain limits to the lessened blood bulk by producing a vasoconstriction which keeps the pressure up. Just how great a diminution can occur before the blood pressure falls cannot be stated, and furthermore this seems to vary somewhat with the individual case". They found that patients who had a reduction in volume to below 70% showed with one exception a blood pressure below normal, the decrease roughly paralleling the amount of the reduction of the blood volume. They concluded that if the blood pressure was below 95 mm. the volume was probably under 70%, and if the pressure was 80 mm. or less, the volume was probably reduced to 60% or less (56).

We see, then, that these investigators were not able to attach much significance to blood pressure values until the blood volume dropped to 70% or below; and as we shall find later (p.36), a volume this low indicates more than a mild state of shock. In the early cases or in moderate degrees of shock, where preventive measures can do most good, the blood pressure is not a reliable guide; and it

is in just these cases that a good criterion is very desirable, since the vasomotor mechanism which has adapted itself to the diminished volume of blood may in any individual case be very near the margin of its compensatory power. Any increase in the load at such a time, such as from anesthesia, surgery, infection or more hemorrhage, may cause a failure of this mechanism with a resulting fall in the blood pressure (Robertson,56).

On the other side of the question, a rise of blood pressure in a shocked patient, produced by intravenous therapy, is not a dependable sign of improvement. Mac Lean said that "To raise the peripheral blood pressure accomplishes nothing save a mechanical effect. A raised blood pressure is not life. In a severely shocked patient the saline runs into the tissues from the blood, and you are left as poor as before. Even blood, let alone Hogan's gelatine solution or Bayliss's gum acacia solution, will do but little more; it, too, disappears into the tissues" (1).

Diminution of the Blood Volume in Shock

As evidenced by the percentile values of blood volume which I have quoted above, an experimental method of determining this factor had been perfected by this time, and the hypothesis of decreased blood volume in active circulation was now a proven feature of the shock picture.

The earlier investigators assumed the blood volume to be diminished as a result of such observations as the clinical improvement which often resulted from intravenous therapy (Malcolm, p.18) and the lack of blood in the heart and great vessels of animals reduced to a state of shock (Mann, p.24). Dale and Laidlaw (24) report: "If the chest is opened, under continued artificial respiration, it is seen that the heart is indeed beating strongly, but that its chambers contain remarkably little blood. Compression of the ventricles between the fingers causes scarcely a movement of the mercury in the arterial manometer. The venae cavae and the portal vein are seen to be flaccid and half empty. The arteries, both large and small, similarly contain but little blood, and appear to be constricted rather than dilated. The liver is moderately pale and certainly not distended with blood, and the same is true of the spleen."

Cannon said, only a short time before the concept of diminished blood volume was proved, "The view developed in the foregoing discussion, that in shock the circulatory difficulty is due to loss of blood from the circulation, though not from the body, is one which has been growing in recent years, as experimental data have accumulated." He suggested the term "exaemia" to emphasize this characteristic of shock (9).

The most important work done in actually demonstrating the lowered blood volume was by Keith, using the dye method devised earlier by himself, Rowntree and Geraghty (39). These authors found that a certain complex dye, called vital red, when injected into the circulation was not absorbed by the tissues and was excreted only slowly by the kidneys. In a few minutes after injection of a known quantity of the dye, therefore, it will be uniformly mixed with the blood, and the dilution of the dye in a specimen of blood taken at this time can be determined by colorimentric methods. From the dilution, the volume of blood in circulation can easily be calculated.

Keith found that the total blood and plasma volumes were consistently reduced in shock, "thus explaining the anemic condition of the patients in spite of a relatively high blood count. Further, it was soon recognized that the diminished blood volume bore a definite relationship to the severity of the patient's condition" (37). And not only was the volume diminished, he found, but in cases "when the loss of blood is excessive, or when there is a severe trauma, a shock-like condition follows, which is distinguished by a failure of the normal process of spontaneous dilution". Even without hemorrhage, Keith found, shock may be accompanied by a fall of blood volume; later work by many investigators proves that this is, indeed, a

constant finding in all types of shock.

As a result of his observations on blood volume in shock, Keith divided his cases into three groups on the basis of clinical symptoms and degree of blood volume reduction. These groups are as follows:

	Pulse	BP	BV
i. Compensated cases: general condition good; feels only weakness and pain of wound. Often very pale, and may have had moderate bleeding. BV never less than 80%; seems to be maximum decrease seen without marked untoward symptoms.	90-110	100mm+	80%+
ii. Partially compensated cases: general condition not good. Usually has had "smart hemorrhage". Very pale, restless, thirsty, vomits readily. Extremities cold and partly anesthetic. Pulse weak and rapid; difficult to count.	120-140	90mm—	65-75%
iii. Uncompensated cases: extremely serious condition. Restless, very thirsty, vomit immediately on giving fluids, extremities very cold to touch. Pulse imperceptible; must take heart rate by auscultation.	120-160	60mm—	65%—

(Keith,37)

Keith's findings have been confirmed by all who have studied the circulating blood volume in secondary traumatic shock in man and in animals. There can be no doubt, Fishberg states, that diminution of this volume is a constant characteristic of secondary shock (28). It is, in fact, the chief factor in the circulatory deficiency.

Failure of Normal Dilution and Retention. We have seen that Keith recognized that the process of dilution which normally replenishes the circulating volume after a loss of fluid is absent in shock.

In a later paper, he says it seems evident that the reduction of blood volume is secondary to some still unknown primary factor(38). One result of the action of this primary etiological factor, he believes, is the fact that the vascular system is unable to retain the normal amount of plasma if the shock is severe. Here we have stated, then, though not for the first time, two classical features of the oligemia of severe shock: the failure of normal dilution and the fact that blood is not retained in the circulation even after transfusion.

It is evident that the failure of dilution must of necessity be a feature of shock; the very fact that the volume of blood continues to decrease proves that the transfer of fluid must be in the other direction. It would seem to follow that the power to retain added fluids must also be impaired in such a situation; and the results of attempts to increase the circulating blood volume by intravenous therapy showed that this is actually the case. Bayliss concluded, from the results of his trials of various intravenous infusions to replace blood, that "no solution containing salts alone is able to remain in the

circulation. The statement applies to both isotonic and hypertonic solutions....The presence of a colloid possessing the osmotic pressure of those in blood is necessary; of those available, gum arabic in 6% solution is the best" (2). This solution was used extensively during the war, and seemed to give as good results as blood itself; after the war, however, a number of disadvantages were found in its use, and gum arabic fell into disrepute.

In the severe cases of shock, it was found, even whole blood itself gave little benefit (v.McLean,p.33). McNee and his associates concluded that "cases exhibiting the severer degrees of shock die in spite of all the methods of treatment at our disposal. It is the cases of hemorrhage, combined with little shock, that form the successes in resuscitation work" (46).

Wallace observed that one class of case still possessed the power of dilution if the necessary fluid was in the tissues; a second class could retain blood or gum saline introduced into his vessels, though his power of dilution was feeble or wanting; and in a third, both of these powers were lost, and treatment availed nothing (72).

The Problem of the "Lost Blood" in Shock

The question which naturally arises as a result of the establishment of the fact of a decreased blood volume

in shock is "Where is the lost blood in the shocked individual?" Cannon gave this question careful consideration, and excluded to his satisfaction the heart and the large vessels (9). In order to understand the basis for this conclusion, we must first give further consideration to the condition of the vasomotor center and the heart in shock.

Evidence of Vasomotor Activity. I have already described some of the opinions that the arteries and veins were empty (Malcolm,p.17), and also more convincing evidence in the form of actual observations on patients and animals in shock (Wallace,p.25; Dale and Laidlaw,p.34), which were strongly against the theory of vasomotor inactivity. Cannon said that the conceptions of venous stagnation prevalent in the past appeared to have been based on observations of shock produced by traumatizing the viscera (p.25), and in such cases there actually is such an accumulation of blood in the splanchnic vessels. Mann stated that this is a local reaction, and can be produced by trauma or even by simply exposing the intestines to the air (45). However, we have the word of the competent investigators mentioned above that in natural shock produced by wounds of regions other than the abdominal, such congestion is not found, and Cannon adds that this cannot be simply that it was not observed, since the addition to

these vessels of the large amounts of blood "lost" in shock would certainly be easily noted (9). Clinical confirmation is found in the fact that little or no benefit results from placing a shocked patient in a position which would drain the abdominal veins toward the heart.

These views were supported by a large amount of experimental evidence indicating that the vasomotor center remains active in shock. Porter concluded that the results of his experiments were "wholly opposed to the hypothesis that would explain shock by the exhaustion of the vasomotor centers". He was unable to produce vasomotor exhaustion by many hours of stimulation of afferent nerves. Even when an animal was in severe shock, afferent impulses produced a well-marked pressor effect, indicating that the vasomotor center was still active; and stimulation of the depressor nerves lowered the blood pressure by as much as 45%, showing the presence in shock of active vascular tone. Porter stated that these reflexes failed only when the blood pressure fell to such a low level that anemia of the vasomotor cells was certain. He is very emphatic that the vasomotor center in shock is neither exhausted, depressed, nor inhibited (53).

Seelig and Joseph reported also that the vasomotor center was not paralyzed in shock, but in good tone; the ear vessels of a shocked rabbit resisted mechanical dila-

tation when the blood pressure was raised to 80 mm of mercury or higher by intravenous injections of fluid (61). From subsequent work they added that further proof of active tone was furnished by dilatation of denervated vessels of the other ear, used as controls, when the fluid was injected; and by dilatation of the normally innervated vessels as soon as their connections with the vasoconstrictor center were severed (62). Similar experiments by Mann confirmed these results; he stated that the vasomotor center is not depressed or fatigued in shock, but is the most resistant of all the vital centers (43).

Evidence that the Heart Is Competent. Investigation directed at determining the state of the heart in shock has in every instance yielded evidence that this organ is functioning competently, and that shock is not due primarily to cardiac failure. I do not mean to imply that the heart is spared from the deleterious effects of the general circulatory impoverishment; it has been shown that an arterial blood pressure below 80 mm is insufficient to nourish the heart and results in a diminished output of energy by the myocardium (48). In spite of this impairment, however, the force of the heart is adequate, as the following evidence will show.

The results of an extensive study of shocked animals led Mann to report that when these animals are allowed to

die from shock the heart still beats, though sometimes feebly, after the respiration has ceased and the blood pressure is practically at zero (43). Dale and Laidlaw reported similar observations (p.34). Cannon says that he has repeatedly observed the same sequence of events at death in cases of shock in human beings (11).

The effect of restoring fluid to the circulation gives further evidence that the heart in shock retains its efficiency as a pumping mechanism. Crile observed that saline transfusions resulted in slowing of the pulse, increase in the amplitude of its wave, and a rise of the blood pressure to normal levels; these facts have been repeatedly demonstrated and confirmed by others (Moon,48). Even when the blood pressure is raised to a level higher than normal by these transfusions or by large doses of adrenaline, the heart is able to carry the load.

Cannon showed many times that after a shocked animal was killed by asphyxia, saline transfusions and stimulation of the heart with adrenaline and massage would almost immediately raise the blood pressure to 150 or even 180 mm of mercury; the heart maintained this load well, even after having suffered from prolonged shock and asphyxia (11).

We may conclude, therefore, that the heart does not fail in shock, and that it is unable to maintain an adequate blood flow and blood pressure only because of an

insufficient volume of circulatory fluid. Also, no form of vasomotor inactivity plays any part in the circulatory deficiency of secondary shock; there is no pooling of blood in the splanchnic or other great vessels with resultant loss of blood "in currency". I have not found these views questioned by any author since they became firmly established during the period of the War.

Capillary Dilatation and Permeability. Cannon pointed out that inasmuch as in shock the vasomotor center is efficient and the heart competent, an adequate amount of blood in the arteries would be accompanied by a high blood pressure; the very fact that the pressure is low, he stated, signifies that the heart is not supplied with enough blood to fill the arterial system (9).

Having rejected the possibility of the arteries and the veins as the site of the blood loss, Cannon then considered the capillaries. He gave a review of the data on the capacity of the capillary bed, of which the essential points were (a) the hypothesis, supported by a number of investigators at that time and now generally accepted, that only a small part of the total number of capillaries is filled with blood at a given time in the normal animal; and (b) the known fact of distensibility of these vessels (Roy and Brown, e.g., had noted that chloroform could double their diameter, thus quadrupling their capacity).

From these facts Cannon concluded that the capacity of the capillaries was sufficient to contain the lost blood in shock (9).

He next turned to evidence indicating that concentration of the blood occurred in shock. This was first reported by Sherrington and Copeman (1893), who found an increase in the specific gravity of blood from a rabbit's ear after the animal was reduced to a state of shock by ligating the mesentery (30). Other investigators came to similar conclusions; I have described the views of Malcolm (p.17) and Henderson (p.21) to the effect that loss of fluid from the blood stream into the tissues occurred in shock. This problem was carefully worked out and confirmed during the War by Cannon, Fraser and Hooper, who found that a constant characteristic of shock was a high concentration of erythrocytes in the capillary blood. The red count was found to roughly parallel the degree of the shock, and in severely shocked patients it was from six to eight million cells per cubic millimeter of blood. As we should expect, the hemoglobin and hematocrit determinations were correspondingly increased, and also the viscosity. Venous counts taken on the same patients, on the other hand, were approximately normal; thus the capillary count was as much as two million cells above the venous count in severe shock (this discrepancy, however, has not

been confirmed by other workers; Moon states (48) that the venous blood is just as concentrated as that in the capillaries). It was noted that the blood concentration, if persistent, was an ominous sign, and an increasing concentration was usually a significant precursor of a fatal outcome. On the other hand, a lessening of the concentration coincided with clinical improvement (13).

The concentration of the capillary blood was proof that an accumulation of corpuscles in the capillaries occurred, but did not indicate that the volume capacity of these vessels was increased. Dale and Laidlaw, however, reported an observation by Mann that the volume of blood obtainable by bleeding the shocked animal out through the large arteries and veins showed a deficiency over and above that which would be accounted for by the degree of concentration, and they confirmed this fact in their own experiments (24).

Also, a number of writers had described congestion of the minute vessels of the viscera on opening the abdomens of animals dead of shock, though they agreed that the large vessels were not filled. Dale and Laidlaw reported a "diffuse, dusky congestion" of the bowel (24), and this was confirmed by Cannon (11); and Whipple described conspicuous congestion of the gut and mucosa (75). These observations are in favor of accumulation of blood in at

least the capillaries of the splanchnic area. From these observations and the other evidence described, Cannon concluded that stagnation of blood in the capillaries accounted for at least part of the diminution of circulating blood volume in shock.

Definite evidence of another source of blood loss is the concentration of the blood remaining in the vascular channels. Since this could result only from a loss of the fluid elements from the blood stream, we are safe in concluding that such extravasation must occur; and since the plasma protein content of the remaining blood is not greatly increased, the fluid which leaves the vascular channels must have approximately the same composition as the blood plasma.

The available evidence was interpreted by Cannon and his co-workers as indicating that in traumatic shock there is a widespread increase in the permeability of the capillaries, resulting in the transudation of plasma and a consequent decrease in the volume of circulating blood; and that this decrease is accentuated by stagnation of the blood thus concentrated in capillaries which are widely dilated (9). These views have been confirmed by all subsequent work, and actual pathological evidence of both stagnation and loss of fluid by permeability has been demonstrated (p.64).

Acidosis and the Critical Pressure

The fact that acidosis--in the sense of decreased alkali reserve--was found to be a constant accompaniment of severe shock had led to work on the possibility of this factor playing a part in the production of shock. Cannon found that cases of low blood pressure due to shock, hamorrhage, or infection with gas bacillus had a diminished supply of available alkali in the blood, and, as a general rule, the lower the pressure the more marked the acidosis. The respiratory rate became more rapid as the acidosis increased, until, shortly before death, a true air hunger might prevail (8). However, as a result of the work of Dale and Richards, the factor of acidosis was proved to be a result of the low blood pressure rather than a cause of it. These workers found that the carbon dioxide capacity of the blood could be reduced to a very low figure by intravenous injections of acids with no permanent change in blood pressure; no symptoms of shock made their appearance at any time during these experiments. They concluded that "simple acidosis, in the sense of a reduction of the alkali-reserve of the blood, even though it be severe and prolonged, does not cause shock or, indeed, any perceptible impairment of the circulation or other vital functions in an otherwise normal animal at rest" (23).

On the other hand, it was found that the production of an inefficient circulation gave rise to definite acidosis when the blood pressure dropped below a certain definite point. This point is remarkably constant in different animals and with different methods of lowering the blood pressure (hemorrhage, pithing, mechanical restriction of the filling of the heart, etc.); in every case, acidosis begins when the systolic pressure drops below approximately 80 mm of mercury. This pressure is therefore termed the "critical level" in a falling blood pressure. It is the level at which the pressure is no longer capable of maintaining an adequate volume-flow of blood to the tissues, which consequently suffer from anoxemia.

Furthermore, if there has been a loss of blood, the circulation becomes inadequate before the blood pressure falls to 80 mm; that is, the critical level is raised (11).

Table Showing the Critical Level: effect of hemorrhage on cat, wt. 2340 Gms., blood vol. ± 117 cc.

Time	Arterial pressure	% CO_2 cap'y art'l plasma	% Hb	Total blood removed
5:05	175	48.2	79	11.7 cc.
5:15	154	47.8	80	23.4
5:26	137	45.1	74	35.1
5:36	108	46.0	68	46.8
5:48	87	44.1	68	50.8
5:57	82	44.1	65	55.8
6:06	79	40.2	63	61.6
6:17	66	32.2	59	67.4
6:27	58	28.4	56	73.4
6:52	36	22.0	46	78.4

(Dale & Richards, 23)

We see that a rapid and serious decline of the alkaline reserve begins when the blood pressure falls below 80 mm of mercury. This is coincident with a drop in the basal metabolism; both are due to a circulation which is inadequate to supply the tissues with enough oxygen for their metabolic requirements.

The Ill Effects of Anesthesia

The deleterious effects of anesthesia received further emphasis during the War, and the responsibility of the anesthetic for at least part of the poor results of surgery on cases of shock was recognized. It had been realized previously that chloroform was very dangerous, but ether was also found to be far from harmless (72).

Crile's experiments (1897) had indicated that dogs could be killed by anesthesia alone, when given over a long period, even though the administration had been carefully done. He found good evidence that chloroform was more toxic than ether in this respect (20). The reason for the shock-producing effect of chloroform, as well as of other anesthetics, is strongly suggested by their effect on the capillaries; they have been shown to produce capillary atony (p.43 and Diag., p.109A).

Nitrous oxide and oxygen were found to be by far the safest combination; Bazett says that with this type of

anesthesia there is rarely any sign of shock to be detected. He found the clinical contrast between cases anesthetized with nitrous oxide and oxygen and those receiving other general anesthetics to be enormously in favor of the former. "The employment of chloroform or ether anesthesia for severe septic cases with anemia, and the keeping of the patient a long time in the operating tables," he said, "are both instances of bad surgical judgement. It should not be often necessary to treat surgical shock; surgical shock should be avoided" (4).

Dale found that ether anesthesia had a markedly deleterious effect on resistance to histamine shock. A cat which had been given 10 mg. per Kg. of histamine on the preceding day without showing marked ill effects was killed by an injection of 2 mg. per Kg. after having been under ether anesthesia for two hours. Anesthesia with nitrous oxide and oxygen had little effect on increasing susceptibility to histamine (22).

The Theory of Traumatic Toxemia

The theory of traumatic toxemia has assumed a very important place in our conceptions of the cause of traumatic shock, and it is this theory which is given most credence today as being the nearest approach we have to a satisfactory explanation. It is a plausible hypothesis,

it is supported by a large amount of experimental evidence, and it offers a good explanation of the clinical picture of shock. For these reasons, I think it warrants discussion in some detail.

Clinical Evidence. The approach to the study of this theory was from several different directions at the same time. In the first place, the circumstances under which shock was most frequently seen to occur were very suggestive. Shock appeared most often after wounds caused by the impact of projectiles traveling at high velocity so that their impact was transmitted laterally and produced wide areas of destruction in the tissues surrounding the actual paths of the missiles (Moon,48). In these wounds, muscle appears to be affected more than any other tissue; it becomes a mass of dark brown, crushed matter, without any evidence of vitality. One cannot fail to be impressed by the enormous destruction which even a small fragment of shell will produce (Cannon,11). In many cases neither bone nor any vital structure had been touched.

Furthermore, it was repeatedly seen that isolation of the injured area had a retarding effect on the production of shock. In many cases, improvement in the patient's condition followed early amputation of a hopelessly mangled limb. Other cases developed shock only after removal of a tourniquet from a wounded extremity. Such experiences

as these led to the suggestion that a constrictor be placed around a limb which obviously could not be saved, and left in place until amputation could be done above it (48).

Such observations as the association of shock with small multiple or large single muscle wounds, however, or the shocking nature of operations involving large muscle masses, such as amputations at the hip, could all be explained by other hypotheses, such as that of Crile to the effect that excessive sensory stimuli produced shock. The appearance of shock only after removal of a tourniquet, in a patient whose condition was formerly good, strongly suggested the formation of a toxic substance, and could be less readily explained on a basis of stimulation of sensory nerves.

Quénu summarized the clinical observations of French surgeons as follows: Secondary or traumatic shock does not appear immediately after the receipt of wounds, and therefore is not due to a nervous effect. Shock is frequently well established before infection has set in; hence, it cannot be of bacterial origin. Everything favoring absorption from the wounded area favored the development of shock. It developed most readily when the area of damage communicated with the surface by only a small opening; conversely, when a large area of flesh and skin had been com -

pletely carried away, as by the oblique impact of a large fragment of shell, shock was either slight or entirely absent. It was the experience of French medical officers that early amputation or debridement of wounds minimized the absorption of toxic substances from the areas of injured tissue, and that delay increased such absorption to dangerous degrees (92,a,b). Quénu believed that absorption of toxic products was the chief factor in the primary development of shock.

The loss of plasma into the tissues, in marked contrast to the normal process of dilution seen in cases of low blood volume, and the failure of fluids to be retained when given intravenously (v.p.37), were known facts which lent themselves readily to explanation on a basis of injury to and alteration of the capillary walls by a toxin, but were not easy to explain otherwise.

Significant Features of Histamine Shock. Of great importance in demonstrating the plausibility of the production of a shock-like state by the action of a toxic substance in the blood stream was the work of Dale and Laidlaw on histamine shock. These investigators gave 1-2 mg. per Kg. of histamine to cats under ether anesthesia and produced in this way a condition which was indistinguishable from shock. The initial effect was a steep fall in blood pressure, followed by a rise which often sur-

passed the original level; these changes occurred within the space of a few minutes. There then began a slow but steady fall in the arterial pressure; this continued until a level of about 60 mm. has been reached, when the respirations, which have been growing shallower and more widely spaced, usually die out. Application of artificial respiration does not arrest the fall, which persists until the blood pressure reaches zero. The condition of the circulatory system found on opening the chest and abdomen has been described on page 34 (24).

The condition of these animals resembles shock in many ways, such as the low arterial pressure, arterial constriction, loss of blood volume, concentration of blood, and decreased cardiac output. Dale and Laidlaw believed, as did Cannon, that loss of plasma into the tissues accounted for part of the oligemia, and that much of the remainder of the blood drained away into the capillary network and stagnated there. They explained this as follows: "It seems to us that, while loss of plasma and consequent thickening of the blood, when they occurred, would accentuate the tendency of the blood thus to accumulate at the periphery, the essential cause must be a general loss of the normal tone of the capillary walls. We suppose that, under the influence of large doses of histamine, this capillary tone is lost throughout the body; that the whole of the poten-

tially available capillary channels become simultaneously patent; that the blood percolates into the network of channels as into a sponge" (24).

This conception involved the assumption that histamine caused a loss of capillary tone. In subsequent investigations Dale and Richards found positive evidence that histamine, "and by implication the group of substances having the same type of action," owed their effect on the circulation to their power of obliterating the normal tone of the capillaries. They concluded further that this "poisoning of the capillary endothelium" increased the permeability of the walls, permitting the loss of plasma into the tissues (24).

Experiments of Cannon and Bayliss. As a result of the evidence which had been accumulating that injury and destruction of tissues were potent factors in the production of shock, Cannon and Bayliss made their well-known experiments, which they reported in 1919, investigating the effects of muscle injury in cats. They pounded and severely bruised the muscles of the thigh with a flat hammer, seldom breaking the skin. After a sharp fall at the time of injury, the blood pressure remained level for a while, and then a gradual secondary fall begins and continues until the death of the animal--a pattern very similar to that described by Dale and Laidlaw. The

respiration and the pulse become markedly accelerated during the secondary fall, but later, as the state of the animal becomes worse, their rate steadily decreases until death (14).

As time passed after the traumatization, the muscles underwent much swelling, and at autopsy varying amounts of extravasated blood were found in the spaces between the muscle bundles. "In no case, however, was there sufficient bleeding into the wounds to account, by itself alone, for the effects observed". The appearance of the muscles was strikingly like that of injured muscles seen in shell wounds (14).

With slight variations in the procedure, several important facts were brought to light. When the blood vessels to the leg were tied and the trauma then administered, no shock appeared; this was evidence against the rôle of nervous factors in its production. However, if after a lapse of time even as long as an hour or more following the trauma the blood flow to the leg was reestablished, a fall in blood pressure to shock levels occurred just as if the vessels had not been occluded at the time the muscles were injured. This was strongly in favor of the hypothesis of a toxic substance which produced its effect only when allowed to enter the systemic circulation.

Disarticulation of the legs, with careful regard for

symmetry, and weighing them, proved that the local loss of fluid to the injured area was not sufficient to account for the effects produced. This loss was found to amount to only 11% of the estimated blood volume.

The effect of the depressant substance was apparently limited and temporary, since if the tissue damage was not too great the pressure might fall even as low as 100 mm. and then spontaneously rise; and furthermore, a fall of the blood pressure after trauma, even after it was well established, could be checked by tying the blood vessels. In many cases, it then rose to normal levels.

Massage of the injured muscle increased the rapidity of the drop in blood pressure, presumably by adding to the rate of diffusion of the toxic product into the blood stream.

Finally, though the shock produced by the trauma was not always fatal to strong animals, Bayliss found that the balance could always be turned against them by the added effect of a comparatively slight hemorrhage (3,10).

The Nature of the Toxic Substance. The nature of the substance which produced the depressant effect upon the blood pressure in shock remained unknown. Turck, reporting experiments similar to those of Cannon and Bayliss, concluded that "the phenomena of shock from all my previous experiments and clinical observations were shown to

be due apparently to toxic proteoses formed by the digestion of injured tissues; that is, to 'shock toxins'" (69). He prepared extracts of fresh muscle tissue, allowed time for the occurrence of outolysis, and then injected the preparation into the veins of normal dogs. A large dose thus given resulted in the death of the animal in about three minutes, while a moderate dose produced a typical clinical picture of shock followed by death in a few hours. Small doses produced shock from which the animals were able to recover.

It had been known for some time, in fact, that substances derived from tissues would cause symptoms resembling shock when injected into animals, and would frequently cause death; peptones and other cleavage products of proteins, bile salts, extracts of almost any body tissue, indeed, gave these effects (Moon,48). A marked fall of blood pressure after the injection of brain extracts was reported by Vincent and Sheen as early as 1903 (71); these workers also found depressor substances in extracts of intestines, liver, spleen, testicles, lung, and others. Whipple and his associates obtained a depressor substance from loops of intestine which had been washed free from their contents and then isolated by ligatures from the rest of the bowel; injection of these solutions into animals gave a profound drop of blood pressure and general

collapse. Their conclusion was that death must result from the absorption of toxic products formed in the intestinal loop (75).

In speaking of the substances produced by tissue disintegration, Bayliss said that "we naturally think of histamine, or related compounds, whose action was investigated by Dale, Laidlaw and Richards" (3). No satisfactory evidence of the part played by any definite chemical compound in the production of traumatic shock was submitted, however, during the War period; nor has any such substance been convincingly incriminated up to the present time, although recent work suggests that potassium may exert a toxic influence in shock (v.p.87).

Acapnia and Fat Embolism Rejected

Concurrently with the important work on the theory of traumatic toxemia, investigation of the respective merits of other theories of shock was carried on during the War period, and several of these were proved to be untenable. I have already discussed the work which led to the discarding of acidosis as a cause of shock (p.47).

Henderson's theory of acapnia was also considered, and an abundance of evidence against it was found. In the first place, the vigorous breathing which according to Henderson lowers the carbon dioxide content of the

blood was never observed by Cowell at the front, although he paid particular attention to the respiration of wounded men. Even the severe pain which Henderson considered to cause the hyperpnea was absent in most soldiers immediately after their injuries (82). Furthermore, in cases of excruciating pain from other causes, such as in facial neuralgia, there is not the slightest evidence of shock; the same is true of the most extreme voluntary hyperpnea (11). Janeway and Ewing were able to produce shock by intestinal trauma in dogs whose carbon dioxide content was kept at or above normal level by means of a respirator just as readily as when this precaution was not observed (86). Finally, typical shock can be produced by methods which certainly involve no change in respiration, such as injections of histamine or tissue extracts, or implantation of muscle into the peritoneal cavity (48).

The theory of fat embolism as the cause of shock was likewise found insufficient to explain the known facts. Blocking of the pulmonary capillaries with fat would be expected to cause distention of the great veins and increased venous pressure, and experiments indicate that such is indeed the case (Bissell,79); in shock, on the other hand, there is always an early fall in venous pressure (Moon,48). The production of shock by intestinal manipulation, injection of histamine, peptones, or fat-

lowered body temperature, (b) lowered blood pressure, and (c) diminished blood volume formed the sole symptom complex amenable to treatment. The last two, they said, would appear to be dependent on one another; these two were treated simultaneously either by intravenous gum-saline or by transfusions of blood. The lowered body temperature was combatted by application of external heat and by giving the intravenous injections at a temperature above normal body heat. The treatment of acidosis by the administration of sodium bicarbonate they found to be of no practical value.

These authors favored the theory of absorption of toxic products from injured tissues as a factor in shock, but concluded, with an attitude of commendable reservation, that "muscle damage could not be more than one of a group of the unknown causes of wound shock" (46).

SECTION V

THE POST-WAR PERIOD

Evidence in Support of Traumatic Toxemia

The War had provided an unparalleled opportunity for a clinical study of shock, and as we have seen, this was taken advantage of with much enthusiasm. Following the armistice, the study of shock from the experimental standpoint was renewed. The existing theories were subjected to a critical analysis, and further attempts were made to discover the conditions that prevailed in the organism during traumatic shock.

Observations on the physiology of the capillaries under normal conditions and in shock, made soon after the war ended, gave support to the views of Cannon et al. concerning the possibility of a significant loss of blood from stagnation in these vessels and diffusion of fluid through their walls. Krogh reported that the capillaries in the skin of the frog are supplied with sympathetic fibers which maintain them in a state of variable tonic contraction (40); this gave credence to the hypothesis that a toxic substance which destroyed the tone would produce a great increase in the capacity of the capillary bed. Later (1929) he described conges-

tion, edema and capillary hemorrhages in the viscera as the characteristic effects of capillary poisons (49).

Erlanger and Gasser found definite evidence of accumulation of blood in the small vessels of the splanchnic area in animals dead of histamine shock. They described "tremendous engorgement of the capillaries and venules of the villi of the intestines" (27).

At about the same time, Rich made careful studies of the capillaries in histamine shock, both in vivo and by microscopic examination. By observations of the vessels in the web of the frog's foot, he found that histamine exerted a local dilator effect upon these vessels and that there also occurred an opening up of large numbers of capillaries of which no trace can be seen before giving histamine. "When injected intravenously in amounts sufficient to produce shock," he says, "histamine gives a quickly progressive dilatation of both the visible and the occult capillaries and their immediately adjacent arterioles and venules, all of which become engorged with blood that moves through them in a strikingly sluggish manner. The circulatory failure of histamine shock results from dilatation of the peripheral vascular bed." (54)

Moon and Kennedy made experiments on dogs which convinced them of the fact of capillary engorgement and

also definitely favored the toxic theory of shock. They produced shock by sterile filtrates of both normal and traumatized muscle injected into the peritoneal cavity, and sterile muscle substance implanted there; these methods avoided the confusing effects of local injury and hemorrhage. The animals gradually developed prostration with low blood pressure, rapid weak pulse, rapid respiration, cold extremities, elevated red count, and high specific gravity of the blood. These features progressed until death in many of the animals. The results obtained were similar in all cases: gross and microscopic examination of the various organs showed widespread dilatation and engorgement of the capillaries, especially marked in the lungs, the gastro-intestinal tract, the liver and the kidneys; a definite contrast to the pallor and anemia seen after hemorrhage. Petechial hemorrhages and edema were present, and frequently effusion into serous cavities; these were considered as evidence of increased permeability of the walls of the capillaries. Similar results were noted in autopsies on human subjects dead from shock as well as in dogs killed by shock induced by traumatizing the extremities (49). The physiologic disturbances in all these cases were the same, leading the authors to conclude that shock resulted from the effects of toxic products absorbed from

injured tissues and that the decreased blood volume was the result of dilatation and increased permeability of the capillaries and venules.

Moon was unable to confirm the findings of Cannon and his co-workers as to a difference between the red counts of capillary and venous blood (see p.44). The concentration of venous blood, Moon found, paralleled that of capillary blood (48). I have found no mention of a discrepancy between capillary and venous counts since Cannon's work (1917), and I think we can conclude that the blood concentration is generalized.

The Theory of Local Loss of Fluids

The chief theory of shock which came into prominence after the war in opposition to the toxic theory was the conception of local loss of fluids into the traumatized tissues as a cause of the oligemia. This conception appeared as early as 1917, when Mann stated that the dilatation of splanchnic capillaries and venules following visceral trauma was a local loss of fluid to the traumatized areas (45).

The chief exponent of this theory, however, was Blalock, who began his long series of experiments in 1927. He repeated the muscular trauma experiments of Cannon and Bayliss, with additional variations "to test

the various theories which have been advanced in an effort to explain the initiating agent in the development of a low blood pressure after gross trauma" (5).

A number of interesting conclusions resulted from this work. In the first place, Blalock states that he was unable to reduce the blood pressure to a state of shock without the loss of enough blood volume into the traumatized area to account for the decline; a loss which sometimes amounted to nearly 50% of the calculated blood volume. He found that there was a proportionately greater loss of plasma than of red cells, accounting for the concentration of the blood. The failure of Cannon and Bayliss to note loss of significant amounts of blood was attributed to the fact that they disarticulated the legs at the hip before weighing; Blalock did a mid-abdominal amputation and split the lower half of the body along the midline, thus including in his weight differences the fluid accumulated in the flank and groin.

Cannon and Bayliss based their toxic theory partly upon the fact that no shock appeared after traumatization of a leg isolated by a tourniquet until the latter was removed. But Blalock found that the development of shock in such cases did not require the return of blood from the extremity, carrying with it the supposed toxic

substances, but only the patency of the femoral artery so that loss of fluid into the injured tissues might take place; for traumatization of a leg which was constricted except for this artery resulted in shock. Like Cannon and Baylies, he found that if both the artery and the vein were included in the tourniquet no shock appeared; he attributed this to the fact that access of blood to the tissues was prevented. Finally, he obtained no fall in blood pressure by the transfusion of blood from a shocked dog into a normal dog or another shocked dog, but rather a rise.

In conclusion, Blalock states that his experiments give no support to any of the other suggested causes of shock, but they are suggestive of the mechanism of shock in wounds involving large muscle masses. He adds that it is doubtful whether the effects of the anesthetic and trauma of surgical procedures would be sufficient to give shock on the basis of local fluid loss (5).

Parsons and Phemister obtained similar results at about the same time. Producing shock in dogs by trauma of the leg, they found that a drop in blood pressure was accompanied by increased volume of the limb and anemia caused by "hemorrhage into the wounded tissues;" they concluded that this "hemorrhage" was the chief fac-

tor in circulatory failure. They found no evidence of a toxic product; extracts from the traumatized limbs gave a negligible drop in blood pressure when injected into normal dogs (50).

Wilson and Roome investigated the effects produced by prolonged constriction of an extremity without trauma. Following release of the tourniquet a state of circulatory depression resulted, varying in severity with the length of the constriction and invariably ending in death if the latter was longer than six hours. At necropsy, the leg was swollen and boggy, and a "local loss of part-plasma fluid, sufficient in amount to probably cause death," was demonstrated by weighing. These investigators concluded that the "withdrawal of water and plasma proteins into the leg to produce the swelling" was the chief factor in causing the inadequate circulation (77). They also found no confirmation of the toxic theory in the action of extracts from traumatized limbs; injection of these into a normal dog gave no fall in blood pressure, but rather a rise (76).

Critique of Methods Used.

The work which I have described represents only a small part of the investigation done on the theory of toxemia and that of local fluid loss, but it will give

some idea of the lines along which these efforts were directed. However, Loon points out that we must not accept the results of such experimentation as above criticism, and gives several examples of interpretations which are open to considerable suspicion. In the last experiments described, for instance (77), it is not possible to separate the effects of actual hemorrhage into the tissues, resulting from the trauma, from the stagnation and increased permeability which the authors are desirous of demonstrating. Also, the failure to reproduce the effects of shock by transfusion of blood from a shocked animal does not mean that shock is not due to the action of a toxic product in the blood stream, although it has been interpreted by several authors as evidence against the existence of a toxin (Blalock, p. 68; Parsons and Phemister, 48; Smith, 73, et al.). The development of an advanced state of shock requires many hours, and the fact that an effective quantity of toxic substance is not present in the blood at one time does not preclude the possibility of this mechanism. And finally, the anesthesia itself doubtless contributed to the picture in many instances; effective doses of barbital in themselves are often sufficient to give symptoms of shock (48).

Neurogenic Factors in Shock

As I have indicated in discussing the conceptions of shock which were held prior to and at the turn of the last century, the nervous factor as an explanation of shock is practically as old as the recognition of its clinical picture. Aside from the early vague ideas such as "functional concussion" or "diminution of nervous fluid", several well formulated theories appeared; the reader is referred particularly to the views of Crile, Malcolm and Boise (pp. 15-18).

Vasomotor Exhaustion from Sensory Stimuli.

Among these theories, that of Crile is outstanding in having as its basis a tremendous amount of painstaking experimental work extending over a period of twenty years. His theory as originally proposed was that shock resulted from excessive stimulation of sensory nerves by what I have referred to in this paper as "shock-producing factors"--namely, trauma, pain, cold, fear and worry, etc.; and that the nocuous or "noci-ceptive" impulses thus aroused led to exhaustion of the vasomotor center. He reported degenerative changes found in the cells of the vasomotor region and believed they were evidence of this exhaustion. He claimed that although a general anesthetic effectively prevented the effects of fear

and pain from reaching the psychic centers during an operation, the noci-ceptive impulses from operative stimulation were not prevented from exercising their harmful effects on the brain. To exclude these impulses, he advocated regional anesthesia or nerve block in addition to general anesthesia, and stated that he was unable to produce shock by trauma to the protected regions of animals anesthetized in this way (21).

However, I have found in the literature practically no agreement with any of the views expressed by Crile; the vast majority of the authors who mention his work take active issue with his tenets. I have described previously the evidence against the hypothesis of vasomotor exhaustion and, in fact, Crile himself admitted later that "this conception did not adequately explain all the phenomena of shock" (21). With regard to the changes in the nerve cells which he reported, these have been confirmed by some investigators; but others have denied that they exceed the limits of normal variations, and in any case, as Cannon points out, they are much less likely to be the cause of shock than a result of the anoxia which occurs in shock (11). Concerning the possibility of harmful effects from impulses when the animal is under general anesthesia, Cannon cites work of Forbes and

Miller which shows that this does not occur when the anesthesia is deep enough to abolish reflexes (11); and several writers have reported failure to produce shock in the anesthetized animal by hours of traumatization of the great nerve trunks (43). Speaking of operations on human patients, Phemister and Livingstone state that if hemostasis and anesthesia are perfect, extensive stimulation of afferent nerves does not seem to be productive of circulatory embarrassment. They give as an example the absence of shock in extremity operations under bloodless constriction and gas-oxygen anesthesia, although excision, chiseling and handling of tissues may be extensive and prolonged (52).

I think we are able to conclude, therefore, that the theory of nervous exhaustion has been discredited. However, this does not diminish the importance of Crile's recognition of the part played by the "shock-producing factors", although subsequent work, which I will now describe, indicates a different mechanism for their action.

Sympatho-Adrenal Hyperactivity.

A relationship between shock and adrenalin production has long been considered. In 1915 Corbett reported the finding of a greatly diminished epinephrin content of the adrenal glands in shock, and concluded

that shock was "a composite in which epinephrin exhaustion and oligemia are predominant factors. Anesthesia, pain, fright and trauma are immediate agents in producing epinephrin exhaustion as well as shock" (17).

Bainbridge and Trevan were the first to report shock resulting from injections of adrenalin (1917). Cannon, however, (1923), dismissed the adrenalin factor on the grounds that the amounts of this substance used to produce shock were far in excess of any possible physiological production and that vascular tone was not dependent upon the production of adrenalin (11).

I have described evidence that the arteries are strongly constricted in shock. In 1917, Erlanger et al. again called attention to this fact, and suggested that a causative factor in shock was the reduced circulation brought about possibly through the action of pain stimuli, and of a certain amount of hemorrhage, on the vasoconstrictor mechanism. They succeeded in decreasing the quantity of circulating blood by rather large doses of adrenalin injected over a period of nearly half an hour, but were not able to produce by stimulation of the vasoconstrictor center sufficient vasoconstriction to cause shock. After sufficiently large doses of adrenalin, they reported, the arterial pressure slowly and steadily

declined until death occurred. The cause of this was thought to be extreme slowing of the blood flow from the constricting action of adrenalin on the arterioles (37). Of interest in this connection is the fact that these investigators and numerous others were able to produce shock simply by mechanical obstruction to the circulation, such as by partial occlusion of the aorta by a clamp for several hours; in these experiments, however, shock developed only after the obstruction was removed (48).

In 1933, Freeman confirmed the action of adrenalin in lowering blood volume. By continuous injection of adrenalin at the physiological rate of output from the adrenal glands in response to painful stimuli, he succeeded in lowering the blood volume as much as 27% in two hours. Preliminary administration of ergotoxine, which is known to block the vasoconstrictor action of adrenalin and the sympathetic nervous system, prevented a drop in blood volume (31).

In order still further to implicate the sympathoadrenal system in the production of this vasoconstriction, Freeman used cats in which a state of "sham rage" had been produced by destruction of the cerebral cortex, as described by Cannon. Such animals are found to "display to a supreme degree the physiological phenomena of

rage, with lashing of the tail, protrusion of the claws, dilation of the pupils, erection of the hairs of the back and tail, rapid heart rate, rise of blood-pressure, and greatly increased secretion of adrenine. The sympatho-adrenal system, in short, is stimulated in a natural manner continuously and excessively for two or three hours, until the animal succumbs" (12). Freeman found that this state was accompanied by a decrease in blood volume identical with that produced by adrenalin, both fluid and cells being diminished; and furthermore, that this was abolished by ergotoxine, though an increase in the heart rate proved that there was still an increased secretion of adrenalin.

Freeman offered the explanation that this decrease in blood volume was due to increased capillary permeability resulting from more or less asphyxia caused by prolonged contraction of the arterioles, and concluded that "prolonged vasoconstriction of itself results in a loss of blood from the circulation."* He considered this very significant in view of the fact that the "shock-producing factors" have in common the physiological ac-

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*Let me again call the reader's attention to the views of Malcolm, probably based upon clinical observation but remarkable for their resemblance to this conclusion of Freeman. (p.17)

tion of stimulating hyperactivity of the sympatho-adrenal system (31). Another fact which seems to me to be very suggestive in this connection is the raised blood pressure which was present in wounded soldiers soon after their injuries (p. 30).

The Nature of Primary Shock.

It seems most appropriate to consider primary shock under the heading of "Neurogenic Factors", since these appear to play the predominant part in its etiology, and to attempt to clarify the relationship of primary shock to secondary shock. Occasional reference has already been made to this relationship in the discussion of the development of knowledge concerning secondary shock (pp. 4,7,11,14, and 29); a review of these will refresh the mind of the reader concerning the essential features of primary shock, including an agreement as to its immediate onset.

Moon states that "primary shock is interpreted by most writers as analogous to syncope, a temporary circulatory disturbance of vasomotor origin. It comes on immediately after wounds, whether trivial or serious, and except in the latter, prompt recovery is to be expected. Emotional reactions to fear, pain and the sight of blood are prominent exciting factors" (48). For example, it may be seen in the man with a perforated peptic ulcer who drops in his tracks (38); in a patient

has received a violent blow on the abdomen (47); in the soldier with severe multiple wounds, who sinks rapidly and dies (18); and in the soldier who is merely shot through the hand, and recovers quickly when warmed and rested.

The very rapidity with which the symptoms of primary shock develop, Fishberg says, speaks strongly for their nervous origin (38). This writer accepts as a cause the pooling of blood in the splanchnic areas, with consequent failure of the cerebral circulation resulting in unconsciousness, as described by Goltz (p.14). A number of others are satisfied with this view, such as Blalock (6), Dale and Laidlaw (24), Coonse (16), et al. Moon also favors a disturbance of vasomotor origin, but suggests Freeman's work on the sympatho-adrenal system as a more probable explanation (48).

Phemister and Livingston divide the causes of primary shock into (a) psychogenic, which operate through mental action on centers in the medulla, and (b) neurogenic, through the action of afferent somatic or autonomic impulses reaching centers in the medulla. The patient who faints when blood is drawn for a Wasserman, or whose blood pressure drops to shock levels from fright during a minor operation, is a case of psychogenic shock. Examples of the neurogenic type are the

early, rapid and alarming falls in blood pressure which may occur in abdominal operations. These writers state that these primary reactions are ordinarily transient and of minor importance, but rarely they may be severe. They conclude that "Primary and secondary shock should be recognized on the basis of difference in etiology rather than difference in time of occurrence" (52).

Conclusions Regarding Primary Shock.

According to the literature, as we have seen, the neurogenic factors, with the exception of the action of trauma, pain, cold, etc. on the sympatho-adrenal system as described by Freeman and Cannon, seem to play a part in the etiology of only primary shock. However, since the prolonged circulatory disturbance seen in primary shock following severe wounds, whatever its etiology, must contribute to the later appearance of secondary shock, the nervous element as a factor in secondary shock must still be considered in this type of case.

In summarizing our knowledge of the etiology of primary shock, I may say that all the opinions I was able to find agreed that this type of shock is of nervous origin, and the great majority said only that the work of Goltz appeared to offer a satisfactory explanation.

This explanation, it seems to me, is entirely ade-

quate in the cases of insignificant and transient circulatory collapse incident to minor injuries; this type of primary shock is nothing more than ordinary fainting.

It is not so easy to accept vasomotor relaxation as the sole cause of the grave and often fatal circulatory collapse which immediately follows certain cases of severe wounds. These cases are clinically identical with secondary shock, except for their early onset; they may grade imperceptibly into secondary shock or they may terminate fatally within an hour. I am reluctant to accept vasomotor relaxation as the sole and entire cause of this type of primary shock when the same relaxation appears to play no part at all in secondary shock which the primary type so closely resembles.

On the other hand, if it is true that the drastic effects of such severe injuries can produce a long-lasting splanchnic dilatation, the result would certainly be a situation in which the effective blood volume would be lowered; and this would indeed lead to typical shock, though from a cause entirely different from those operating in secondary shock.

As an alternative explanation, we have Freeman's hypothesis of hyperactivity of the sympatho-adrenal system, which is known to produce a decreased blood volume under experimental conditions. This appears to me to be

a more reasonable explanation, partly because it is probably a factor in secondary shock; I can see no grounds for the common assumption that these two types of shock, which so exactly resemble each other in every way save time of onset, should have different etiology.

However, the observations of Fraser and Cowell that blood pressures taken as early as possible on serious cases of primary shock in the War were always low (see p. 30) seems to favor vasomotor paralysis rather than Freeman's theory as a cause of this type of shock.

I may conclude that we know practically nothing of the causes of primary shock. Fishberg says that the entire conception of vasomotor relaxation as a cause of this type of shock in man is as yet largely theoretical, and points out that the subject has been little investigated because patients usually either rapidly succumb to primary shock or recover in a short time (28). Stanbro concluded (1936) that the cardinal reason for the symptoms of immediate shock has never been interpreted (67), and in this I think we may agree with him.

The Adrenal Cortical Hormone in Shock

We have seen that the part played by adrenalin in the production of shock was dismissed as negligible by

Cannon in 1923, but that recent evidence indicates that hyperactivity of the sympatho-adrenal system may well be a factor in the cause of the shock syndrome.

The very close resemblance between the signs and symptoms of shock and those produced by extirpation of the adrenals, known to be a result of cortical hormone deficiency and not of adrenalin lack, led to a consideration of the cortical side of the adrenal question. In 1926, Rogoff and Stewart reported on the effects of adrenalectomy in dogs: these animals, they said, may remain in good health for a time, but a rather abruot development of characteristic signs and symptoms inevitably follows, and terminates in death. At autopsy, marked congestion of the viscera was found (57).

Swingle and his co-workers kept such dogs alive and in perfect health by giving them cortical extracts (1933). When this treatment was discontinued, a fall in blood volume and blood pressure occurred and progressively increased until the death of the animals. Hemoconcentration, increased viscosity of the blood and a high red cell count were present. "The animals appear to be unable to draw fluids back into the blood stream; this failure of normal dilution is the essential point in uncompensated traumatic shock and in adrenal insufficiency. The similarity of the cardinal features is too evident to

be ignored." These authors consider their experiments to prove that the function of the cortical hormone is the regulation and maintenance of a normal circulating volume of blood, and its lack causes loss of fluid through the capillary walls. On this basis, they suggest that the use of cortical hormone in the treatment of shock deserves investigation (68).

These experiments proved conclusively that shock following removal of the adrenals was not due to a lack of adrenalin, but to cortical insufficiency. Swingle listed a large group of findings which are common to this type of shock and to traumatic shock; these include all of the important characteristics of both. (see table, p.104A).

There is one important difference, however, between traumatic or surgical shock and the shock resulting from cortical insufficiency: this is the late onset of the latter. Shock develops within a few hours after trauma or burns; but when the protection of adrenalectomized dogs by injections of cortical extracts is discontinued, the development of a severe state of shock and death requires several days--an average of 7 days, according to Stewart and Rogoff (48).

Soon suggests that a possible explanation is the hypothesis that one function of the cortical hormone is to maintain the tonus of the capillaries and venules.

When deprived of this hormone for a time, or when it is considerably reduced in quantity, these vessels would become atonic and relaxed, and would then become abnormally susceptible to the agents and conditions which produce shock. Thus insufficiency of the cortical hormone might cause shock indirectly by increasing the susceptibility of the organism to shock-producing factors (48).

The credibility of this hypothesis is increased by the high susceptibility to injurious agents and adverse conditions in general which is found in animals whose supply of cortical hormone has been decreased, or in Addison's disease. Such subjects are hypersusceptible to the actions of drugs and toxins; they are unable to withstand extremes of temperature, anesthetics, minor surgical procedures; they succumb easily to slight infection. And the similarity of the signs and symptoms of these conditions to those of shock, described above, is very suggestive (48).

Several authors have observed beneficial results from the use of cortical extracts in shock. Dragstedt and his collaborators found that the severity of anaphylactic shock in dogs was decreased by the administration of cortical extract two to six hours before the shock was produced. If given later, after the shock had developed, little improvement was noted (25). Perla

likewise found cortical substance--desoxycorticosterone --was more effective as prophylaxis than as treatment of experimental shock in dogs (51). Weil corroborated the action of these substances in preventing shock (74). Selye described as "counter-shock" the changes which occurred in an animal in the process of recovery from shock. He found that adrenalectomized dogs in shock required more cortical extract to produce these counter-shock phenomena than did normal dogs in shock; from these results he concluded that "the signs and symptoms of shock are at least partly due to adrenal cortical insufficiency." (64). Heuer and Andrus made careful tests of the properties of cortical extracts in shock produced in dogs by injection of extracts from closed intestinal loops. When the cortical extract was injected at the same time as the loop extract, the resultant shock was much less severe than in controls. When a state of profound shock was allowed to develop after the injection of loop extracts, neither blood transfusion nor cortical extract alone caused any degree of improvement, but a combination of the two produced "a markedly beneficial and even striking effect in eventually raising the blood-pressure to nearly the normal level and maintaining it, in restoring the plasma volume and preventing the subsequent loss of the

fluid elements of the blood, and therewith prolonging life" (33).

All of the authors just quoted agree upon the benefits resulting from the use of cortical extracts in shock. Only one of them, however, even ventures the opinion that insufficiency of this material plays any part in the production of shock; and nowhere do we find the expression of any ideas as to why the cortical hormone might be low in shock or by what mechanism it might produce detrimental effects if it were insufficient. We are forced to admit, then, that the only evidence thus far advanced in favor of a cortical hormone factor in shock is (a) the fact that the symptoms and signs of known cortical insufficiency are strikingly like those of shock and (b) the good results achieved with cortical hormone therapy; and not even the latter can yet be said with certainty.

The Plasma Potassium in Shock

The latest work on shock presents the hypothesis that the syndrome is accompanied by a rise of plasma potassium which is to some extent a cause of shock, and that the beneficial effects of treatment with cortical hormone are due to the action of this substance in lowering the potassium level. This is the first evidence

of a reasonable explanation of the improvements which have resulted from the use of cortical extracts in shock.

Zwemer and Scudder (1938) report that their impression, "based on thousands of potassium determinations in a number of animal species and man, is that plasma potassium is remarkably constant and difficult to alter for long," but that despite this apparent stability, increases may be expected after severe tissue damage or extracellular fluid depletion--that is, in situations such as those which lead to shock. They go so far as to suggest a relationship between the potassium level and the histamine-like substance released by tissue injury--now generally termed "'H' substance"; for they state that "It is probable that potassium is an important 'H' substance always available." Thus we have a definite substance suggested as being the long sought "toxin" of shock (78).

Scudder states that a rise in the plasma potassium level has been demonstrated by a number of authors, in various kinds of shock, whether produced by tissue abuse, loss of fluids, hemorrhage, injections of toxic substances, destruction of the adrenal cortex, anaphylaxis, or various intestinal manipulations or obstructions. He stresses the point that this alteration of

potassium is only one of the variables in shock, but that its increase serves as a measure of cell injury, thus tending to parallel the severity of the change (60).

The accompanying table shows the changes in the potassium level in several of the experiments of Zwemer and Scudder:

Cat No.	Initial K, mg %	Procedure used to produce shock	K in shock, mg %	Time of survival
3644	27.5	Trauma under amytal	(24.7;no shock produced)	
3640	28.1	Severe trauma c "	36.5	4 hrs.
3630	27.5	Jejunal loop	39.3	14 hrs.
3631	20.2	20 cm streng'd loop	66.6	30 hrs.
3713	22.7	Duodenostomy	44.2	5 days
3639	21.8	Duodenal obstruction	39.7	3½ days

(78).

It is notable that in No. 3644 trauma to both legs failed to produce shock. Also, in several experiments where repeated small amounts of blood were drawn until the cat died, the potassium level remained quite stable until the blood pressure dropped very low--to around 40 mg --and only then did it show a rise; and the blood specific gravity, which before had been dropping as dilution occurred, then began to rise, indicating beginning concentration. These points indicate the relative stability of the potassium level (78).

In the normal state, it is well known that there is very little potassium in the plasma or the intersti-

tial fluid, where sodium is the cation which is vastly predominant. In the cell fluid, on the other hand, the reverse is true; almost no sodium is present, and a great majority of the cation is potassium. A similar relationship exists between the one-celled sea alga Valonia and its environment, and Osterhout proved that this cell dies when the concentration of plasma in the water is raised to equal that of the cell fluid (89). Of interest in this connection is the high concentration of potassium which is found in the fluid surrounding injured muscles. No definite conclusions can be drawn from these facts, but they are at least suggestive of the possibility that changes in this relationship may accompany or even cause tissue injury (60). Zwemer and Scudder state that "Since a marked increase in extracellular K is injurious to cells and injured cells lose K, a vicious cycle ending in death may be initiated if the plasma K is allowed to rise" (78).

Scudder points out that potassium is known to be a toxic substance, and that relatively small doses administered to animals will cause death. An increase in this ion first stimulates all types of muscle, then paralyzes it as the concentration becomes higher. Aubert and Dehn (1874) observed in dogs that small doses

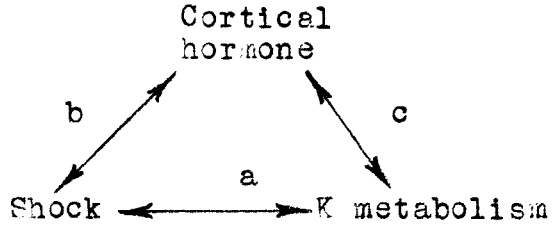
caused a rise in blood pressure while larger amounts caused a fall. Kleeberg (1903) noted a fall with intravenous injection of less than 3 mg per Kg (60).

Scudder gives the blood findings in 37 cases of shock in human patients due to operation, auto and other accidents, burns, etc., and says there were no survivals in those cases having an increase in plasma potassium of over 100% or a decrease (sepsis) of over 25%. For the whole group, however, although many were moribund and had failed to respond to the usual restorative measures of transfusions, oxygen and saline, he obtained a survival rate of 52% by treatment with cortical extract and saline; these results he considers encouraging (60).

The facts presented thus far, then, are as follows: (i) A rise of plasma potassium is one of the phenomena of shock; (ii) cortical substance benefits cases of shock and lowers the potassium level in these cases; and (iii) removal of the adrenal cortex gives a picture identical with that of traumatic shock. (For the truth of the latter part of ii we have only the statements of Scudder; the rest appear well verified). In addition, it has been claimed that the normal function of the cortical hormone consists of regulation of the blood volume (p.83).

These facts suggest another angle of approach: that is, does the cortical hormone play a part in the regula-

tion of potassium metabolism in the normal animal? Concerning this question, the work of Zwemer and Scudder indicates that potassium regulation is a function of the adrenal cortex, and they state that this conception is receiving increasing support (78). If this evidence can be accepted, we then have three separate relationships, which I will attempt to show graphically by the accompanying diagram:



(a) Potassium level is high in shock.
(b) Cortical hormone is beneficial in shock; its absence results in a typical picture of shock; and it has been claimed (p. 83) that a normal function of the cortical hormone is the regulation of the volume of circulating blood.
(c) Cortical hormone plays a part in potassium metabolism; and it lowers the potassium level in shock.

These interrelationships are so suggestive of cause and effect that they certainly cannot be lightly dismissed. Our knowledge of this subject is still far from complete;; we still have no indication whatever, for example, as to why the secretion of the cortex should be decreased in shock--if, indeed, it is decreased. I think it is not too much to hope, however, that additional work

along this line will substantiate the value of cortical hormone therapy in shock and will perhaps clarify our conceptions of the nature of this phenomenon.

Personal Comment

The discussion of recent work on the relationship of potassium and the adrenal hormone to shock brings to a close my consideration of the theories which have thus far been offered in explanation of this truly perplexing phenomenon. Much has been learned concerning its nature since interest was first stimulated to a high pitch by "the great pandemic of shock" which occurred during the War. Our knowledge of the gross bodily changes which produce the picture of shock may, I think, be said to be fairly satisfactory; at any rate, they afford a rational explanation of the clinical picture. Concerning the finer points, particularly the cell changes which initiate capillary injury and the possibility of arresting these changes, we know very little.

The great disadvantage inherent to a consideration of the nature of shock in a paper of this size is that it must of necessity be influenced by the conclusions of the writer. The literature on the subject is far too extensive to permit a complete abstraction; nor would such a condensed version be an adequate treatment

of the subject. For this reason, I have chosen to accept the work which seemed to offer the best explanation of the facts, and which was generally accredited by the authors I have read, and to consider this work in comparative detail. I believe this has resulted in a more interesting discussion, and certainly one more informative of the methods of investigation which were used, than any attempt at a more complete abstraction.

Thus no attempt has been made to present sufficient information to allow the reader to draw his own conclusions; this is especially true of the negative side of the question, in which I have dismissed with scant formality the views of such men as Crile and Henderson, who worked for many years on the problems of shock. For a more complete consideration of the individual theories, the reader is referred particularly to the books of Cannon and Moon (11, 48).

SECTION VI

SUMMARY OF ACCEPTABLE THEORIES

The principal theories regarding the nature of shock which had been formulated by the end of the war are as follows:

1. Inhibition

2. Reflex paralysis of vasomotor center
3. Vasomotor exhaustion through excessive sensory stimuli
4. Fat embolism
5. Acidosis
6. Acapnia
7. Adrenal hyper- and hypoactivity (adrenal medulla)
8. Vasoconstriction and capillary congestion
9. Traumatic toxemia

I have already rejected the first six of these, and described what I thought was the most convincing evidence against them. My opinion, based on what I have read in the literature, is that none of these theories affords a satisfactory explanation of shock.

The last three of these theories have their counterparts in the present conception of shock. The theory of traumatic toxemia is at this time the explanation to which we can give greatest credence; as far as I know, no facts at variance with this theory have been convincingly demonstrated, and on the other hand, much evidence has served to corroborate it in late years. An editorial in the American Medical Association Journal, 1933, states that this theory is "a satisfying explanation of the genesis of shock", and that it explains all the

characteristic features of shock (36). The same may be said today of many cases of shock, although in a smaller number of cases where shock develops after a relatively slight wound, Toxemia seems to play little or no part as a causative factor.

The present counterparts of the adrenal theories are two: the conception of adrenal cortical insufficiency and Freeman's hypothesis of excessive sympatho-adrenal activity. The latter also represents an explanation of the "vasoconstriction and capillary congestion" theory, which was advanced by several men (e. g. Malcolm, p. 17) but never given a rational basis.

In addition, the theory of local loss of fluid, which received its greatest support from Blalock, and Scudder's hypothesis of elevated serum potassium level have appeared, so that the present list of theories is as follows:

1. Traumatic toxemia
2. Local loss of fluids
3. Hyperactivity of the sympatho-adrenal system
4. Insufficiency of adrenal cortical hormone
5. Elevation of serum potassium

I have given these in the order of the security of the places they occupy as causative factors of shock; traumatic toxemia is accepted by everyone, while the elevation of serum potassium is new and unproven. The evidence is strongly in favor of the conception of sympatho-adrenal hyperactivity, but it cannot as yet be accepted as a proven theory. That loss of fluids in and about the injured area plays a contributory part in lowering the blood volume in at least some cases of shock is, I think, well established. Moon says, in this connection, that "any loss of blood and fluid is of importance when circulatory deficiency threatens, and local loss is a major factor in certain instances" (48).

As regards the hypotheses of cortical hormone insufficiency and serum potassium elevation, they find a place in a list of "acceptable theories" only because they represent new and potentially promising evidence, in which no discrepancies have as yet been discovered. They will bear watching, but require the test of a great deal of further investigation before their actual worth can be evaluated.

I wish to emphasize that in rejecting certain theories of the cause of shock I am not disregarding the value of the contributions to our knowledge of

shock which resulted from the investigations of the men who proposed these theories. Credit is due to all of these workers for the parts they played in advancing the knowledge of this problem to its present status.

It is evident that in the present state of our knowledge we cannot explain shock on the basis of any single theory. This fact is emphasized by a number of recent writers on the subject; Frazier states that "When so many theories are advanced for the explanation of a condition, it is generally conceded that no one theory can be accepted" (30). It is quite probable that the factors which are chiefly responsible for the development of shock under a given set of circumstances may be considerably different from those which cause its appearance under other conditions. Furthermore, a given case of shock is more often the result of a combination of factors than of one cause acting alone, as was observed repeatedly during the war.

In conclusion, therefore, although we have learned a great deal regarding the nature of the shock syndrome, its mechanism and its behavior, I still must admit that our conceptions of the fundamental causes of shock are as yet largely hypothetical and unproven.

SECTION VII

REVIEW OF THE KNOWN FACTS OF SHOCK

At this point it is desirable to briefly summarize the established facts concerning shock, and to offer an explanation of its development. Since most of this material has been considered previously and the few new facts mentioned are easily understood--are, in fact, almost self-evident--on a basis of the evidence I have already presented, I am able to dispense with all but a minimum of explanation in this section.

Shock is of two varieties, primary and secondary. The primary type appears almost immediately after injury, and hence is thought to be largely of nervous etiology; it is usually temporary, and is characteristic of (a) very severe injuries and (b) comparatively trivial injuries in subjects of nervous or "high-strung" natures, where it is comparable to syncope or collapse. Secondary shock appears only after a matter of hours following the injury; it is a result of several factors, which are more or less controllable. An important characteristic of this type of shock is its tendency to progress to death because of the development of a vicious circle of tissue anoxia and capillary atony.

A diminution in the venous return to the heart is

the fundamental disturbance common to all varieties of shock. The cause of this is the decreased volume of blood in circulation; a decrease both in the actual volume, by loss of fluid through capillary walls, and in the effective volume, by dilatation of capillaries and venules and stagnation of blood. Inability of the shocked part to assimulate fluids doubtless also plays a part in diminishing the blood volume, as does loss of fluids by sweating and vomiting.

The "lost blood" in shock is located as follows:

(a) In the capillaries and venules of the extensive visceral areas;

(b) In the tissues of the same areas, in the form of edema fluid of high protein content;

(c) In the traumatized areas, in similar form; and

(d) In the serous cavities, in the form of effusions of high protein content.

It is not in the arteries, which are strongly contracted, nor in the veins, which are collapsed.

The heart remains competent; it has been well established that shock is not due to myocardial failure. Fishberg favors the term "peripheral circulatory failure" for shock, to emphasize the extracardiac origin (28).

The volume output of the heart is greatly dimin-

ished, but this is an inevitable result of low venous return and is not due to inefficiency of the heart as a pumping mechanism. The rate of the heart is increased, often exceeding 140 per min. To partly compensate for the lessened blood supply, a greater part of the oxygen is removed; hence the oxygen content of venous blood is lower than normal, and the arterio-venous oxygen diffusion increased (28).

The vasomotor center remains active, and maintains a state of marked constriction in the blood vessels, particularly those of the splanchnic and peripheral areas. Failure of this center never occurs in shock except as a terminal event.

The blood pressure is not greatly lowered in the early stages of shock, but is nearly always markedly lowered in severe shock. It is maintained in the face of low blood volume only by the activity of the vasomotor center. For this reason, the blood pressure is not an adequate index of the presence of shock; it may be nearly normal in the presence of a seriously embarrassed circulation (Roome, 58, et al.)

A fall in venous pressure is a constant accompaniment of severe shock, and, according to many observers, precedes the drop in arterial pressure. The collapsed peripheral veins make it very difficult to insert a needle.

A rapid, "thready" pulse is typical of severe shock, and results from the circulatory conditions just described. In advanced stages of shock, it is often impossible to palpate the pulse in the peripheral arteries.

Capillary dilatation and increased permeability are caused by injury to the capillaries resulting from a combination of factors such as trauma, cold, and toxic products. As a consequence of these changes, the blood stagnates in the capillaries and undergoes hemoconcentration by loss of fluid through their walls; thus the actual blood volume is diminished and the volume of blood in effective circulation still more reduced. When this results in a drop of arterial pressure to below the "critical level", the tissues can no longer be adequately supplied with oxygen, and anoxia results; the anoxia itself is productive of capillary dilatation and permeability, and thus a vicious circle is created.

Severe shock is characterized by failure of the normal process of dilution and inability of the vascular channels to retain added fluids; these conditions result from the capillary injury when serious or when prolonged for a considerable length of time.

Increased concentration of the blood results from the loss of fluids through the capillary walls; the content of plasma proteins and other solids in this

fluid is less than that of the plasma, so the concentration of these substances in the blood remaining in the vascular channels is increased. This is manifested by the following changes in commonly made blood determinations:

1. Increase in the erythrocyte count, especially of capillary blood, as described previously.
2. Increase in volume of packed cells, per hematocrit.
3. Increased hemoglobin content.
4. Increased plasma protein content.
5. Increased specific gravity of plasma and whole blood.
6. Increased viscosity.

These indications of hemoconcentration are a much more reliable guide to the appearance of shock than the fall in blood pressure, since they occur considerably earlier than the latter. They are also the principal criterion in the differentiation between shock and hemorrhage; it is well known that the concentration of the blood is decreased in hemorrhage by absorption of fluid from the tissues into the blood. This criterion is of practical value, since shock and hemorrhage have many features in common and their differentiation is frequently of clinical importance.

The body temperature in shock tends to be lowered. The most constant finding is that the skin is much colder in relationship to the rectal temperature than in health; but the latter also is very frequently low, especially if exposure to cold was a factor in the production of the shock. The cause of this is twofold: (a) The production of heat is diminished, owing to the diminished amount of oxygen available because of the decreased volume flow of blood, and the resultant lowering of the basal metabolism which is present in severe shock; and (b) the loss of heat is increased because the profuse perspiration favors cooling of the body by evaporation, and in many cases because of exposure to cold.

Certain other factors are apparently a direct result of the inefficient circulation. The acidosis of shock is accounted for by inadequate oxygen supply to the tissues. Acidosis appears when the blood pressure is reduced below the critical level, and this is also true of the reduction in basal metabolism; we would expect these two factors to appear simultaneously, since both result from inadequate supply of oxygen to the tissues. The urinary output is diminished in shock, sometimes to the point of complete anuria, yet the specific gravity of the urine is not raised; this combination indicates kidney damage, which is without doubt a result of the impaired oxygen

supply. The non-protein nitrogen content of the blood is often considerably elevated. The blood chlorides are consistently depleted.

It is convenient to divide cases of shock into three groups on the basis of clinical observation and reduction in blood volume: these are termed (i) compensated, (ii) partially compensated, and (iii) uncompensated.

Certain "shock-producing factors"; namely, trauma, pain, wet, cold, fear and mental anguish, exhaustion, anesthesia and operation, favor the development of secondary shock, or increase the seriousness of shock which is already present. This effect is in direct proportion to the number of these factors which are acting, the severity of each, and the time during which they exert their influence. The significance of this relationship lies in the fact that these shock-producing factors are largely preventable.

The role of hemorrhage in the production of shock cannot be overemphasized. It is evident that since the essential feature of shock is a diminution of circulating blood volume, any direct loss of blood will accentuate the condition. Bayliss found that if muscle trauma failed to produce shock in healthy cats, the additional effect of a slight hemorrhage always did so (3).

I have included this table because it demonstrates the striking similarity between adrenal insufficiency and shock and shows at a glance the main clinical features of the two conditions.

Conditions Existing in Adrenal Insufficiency (Animals) and Traumatic Shock (Man). (Swingle,68)

Blood volume	Decreased
Venous return to rt. heart	"
Cardiac output	"
Rate of blood flow	"
Blood pressure	"
Venous pressure	"
Condition of heart	Apparently normal
Heart rate	Increased
Weak, rapid pulse	Present
Vasomotor center	Apparently normal
Vasoconstriction	Present
Erythrocyte count	Increased
Hematocrit	"
Hemoglobin	"
Blood viscosity	"
Hemoconcentration	"
Ability to dilute	Absent
Basal metabolism	Decreased
Body temperature	"
Alkali reserve	"
Blood N.P.N. and urea	Increased
Urine volume	Decreased
Sensitivity to painful stim.	"
to cold	Increased
to anesthesia	"
to hemorrhage	"
to trauma & operat'n	"
to infect'n & toxins	"
Use of vasoconstrictor drugs	Ineffective
Forcing fluids	Beneficial

Finally, shock is no longer regarded as exclusively a physiological disturbance. Contrary to the opinions of the early investigators, we find at post-mortem definite pathological changes which are adequate to account for the death of the patient. These consist of enormous widening and engorgement of the entire stream bed of the capillaries and venules in extensive visceral areas including the lungs, liver, kidneys, and the mucosal and serous surfaces of the respiratory, gastro-intestinal and urinary tracts. There is often marked edema of these tissues. The mucosa of the bowel is congested and edematous, resembling purple velvet.

Several new hypotheses are supported by recent evidence which appears valid and has not yet been refuted, and these deserve to be provisionally included in this summary.

Probably the best verified of these is the statement of Freeman that the vasoconstriction in shock, formerly generally considered as compensatory to the diminished blood volume, is so marked as to constitute in itself a cause of decreased blood supply to the tissues. This excessive constriction, Freeman believes, is caused by hyperactivity of the sympatho-adrenal system.

Recent work indicates that the adrenal cortical

hormone plays a part in shock, and is very possibly deficient in shock. This substance seems to be beneficial both as a preventive measure and in therapy.

Scudder and others find that the serum potassium level is elevated in shock, and suggest that this substance may be one of the toxins liberated by tissue injury. Scudder believes that the beneficial effects of cortical hormone in shock are due to the action of this substance in lowering the potassium level.

SECTION VIII

THE MECHANISM OF SHOCK

The mechanics by which the circulation becomes deficient are not difficult to explain on the basis of the known facts. Moon points out that the fundamental concept of "an uncompensated disparity between the volume of blood and the volume-capacity of the vascular system" makes the circulatory deficiency understandable, and that the cause of this disparity lies in two groups of factors which usually operate in combination:

I. Those factors which reduce the volume of blood. Loss of blood by hemorrhage decreases the blood volume directly. The decrease may develop indirectly by the transudation of plasma through endothelial walls whose

permeability has been increased by any of the agencies which affect capillaries injuriously; transudation from the capillaries of the extensive visceral areas is doubtless of chief importance, but local loss of fluid to the traumatized area is a significant contributory factor in at least some cases of shock. Perspiration and vomiting augment the dehydration still further.

II. Those factors which increase the volume capacity of the circulatory system. The factor of prime importance here is capillary atony. The potential vastness of the capillary bed has been proved by Krogh, who found that skeletal muscle, for instance, was provided with a capillary supply adequate for maximum activity, and that the number of these vessels which are opened up is greatly increased during activity. During rest, on the other hand, only 1/20 to 1/40 of the capillaries are open to circulation (41). Moon states that the capillaries of the skeletal muscles alone, if simultaneously opened to an average diameter of 8 micra, would contain about five liters of blood (48). The potential volume of the capillaries of other areas is probably comparable to that of the muscles; for example, it is well known that the blood supply to the intestinal tract is greatly increased during digestion.

Under the influence of any agency which affects

capillary endothelium injuriously, the closed capillaries in an area quickly open to normal or super-normal diameters. The volume-capacity of the vascular bed in that area is increased several times; these widened capillaries "withdraw the blood from circulation like a sponge absorbs water." The venous return to the heart is reduced, and with it the volume output; and as a result the tissues suffer from anoxia.

With the development of anoxia, what may be called the primary vicious circle of shock is established, for anoxia in itself is known to produce capillary atony and permeability. Krogh found that anoxia gave a definite increase in permeability in thirty seconds, and irreversible stasis in fifteen minutes, in the web of a frog's foot; other experiments produced dilatation or increased permeability or both (41). Erlanger et al. found that the tissues of the limbs showed a marked engorgement following the release of temporary arterial obstruction (48). The anoxia itself, therefore, maintains and accentuates the very factor which caused the oxygen deficiency--namely, the decreased volume flow of blood; and this in turn still further increases the anoxia.

Thus we see that whenever the blood volume is reduced to the point where anoxia appears, we have estab-

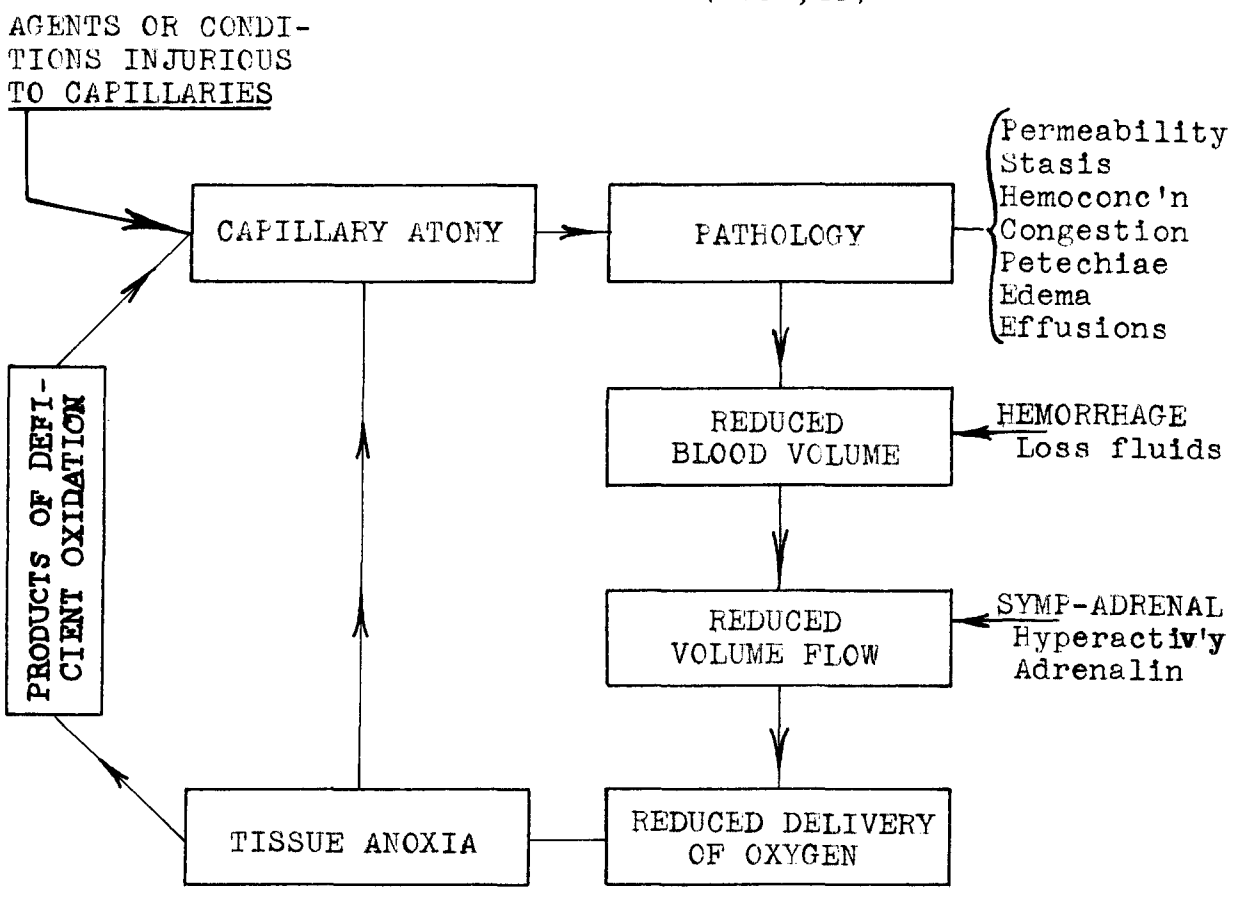
lished the well-known tendency for shock to become progressively worse until death, by the operation of a vicious circle.

The causative factors of shock are the agents by which the development of the vicious circle is initiated. Thus toxic products of tissue injury, regardless of what these substances may be, produce capillary dilatation and permeability, and the diminution of the blood volume is started on its way. The "shock-producing factors" probably owe their action to the production of sympathoadrenal hyperactivity, according to Freeman (p.76); the resulting excessive vasoconstriction decreases the blood supply to the peripheral and visceral areas, tending to give capillary anoxia simply by mechanical obstruction to the circulation. The factor of cold has the additional effect of a direct action in relaxing capillary walls (Krogh, 41).

The marked vasoconstriction, although it probably plays a part in the production of anoxia of the peripheral tissues, is still the only means by which the blood pressure could possibly be maintained high enough to support life in the presence of the low blood volume. By diverting the blood from the peripheral and splanchnic areas to the heart and central nervous system, it provides a blood supply to these vital organs. Its function,

DIAGRAM OF THE VICIOUS CIRCLE IN SHOCK

(Moon, 48)



THE AGENTS OR CONDITIONS INJURIOUS TO CAPILLARIES

Clinical	Experimental
Trauma, burns	Muscle pulp
	Tissue extracts
Extensive surgery	Burns, trauma
	Obstruction to bowel
Intoxications	Peptone, venoms
Drugs	Bacterial products
Metabolic	Bile and its salts
Bacterial	Emetine and other drugs
Serum disease	
Abdominal	
Obstructions	Histamine
Perforations	Anaphylaxis
Peritonitis	Narcotics; barbital, &c.
Pancreatitis	

therefore, is undoubtedly more or less compensatory, and accounts for the fact that the blood pressure is usually not greatly lowered until the shock is very severe.

There is, of course, a limit to this method of compensation, and when the cardiac output falls below a certain indefinite amount the blood pressure begins to drop in spite of maximal vasoconstriction. This results in anoxia of the vital centers in the medulla; the vasomotor center fails and loss of vascular tone will occur as a terminal phenomenon--but never in the early stages. The respiratory center fails, and breathing ceases. The heart is still beating effectively, and may continue to do so after the blood pressure drops to zero. With the failure of respiration, of course, death soon follows.

Thus we see that the mechanism of shock could be comprehended only after the reciprocal relationship between capillary atony and tissue anoxia had been demonstrated. The sensitivity of the capillary endothelium to oxygen lack, Moon states, "provides the self-perpetuating quality in the cycle of death." He believes that many clinical features such as rapid feeble pulse, Hippocratic facies, vomiting, depressed renal function, circulatory collapse, clouded mental state and final semicomatose condition, which are common to shock and to the "toxemia" of many severe pathological conditions,

are probably more anoxic than toxic; simple anoxemia from any cause will duplicate all of these features. Moon reasons that the mechanism of death in shock is not different from that of death from other natural causes; in the former, anoxia originates rapidly consequent to capillary atony, while in the latter it may occur "only as a terminal factor incident to deficiency of a vital organ or function" (48).

These appear to me to be logical conclusions; although they have not as yet been substantiated or accepted, they at least show the modern tendency to think of shock in rational terms rather than as a mysterious and misunderstood phenomenon.

SECTION IX

SITUATIONS IN WHICH SHOCK IS SEEN CLINICALLY

Up to this point I have given little indication of the wide variety of conditions in which shock may be expected. Traumatic or wound shock was the subject of most of the investigation during the war, and post-war work tended to continue along the same lines until recently. I will now briefly consider shock in its clinical aspects, in order that the reader may appreciate the variety of situations in which it may occur.

Shock following accidents, surgery, or hemmorhage: these cases are grouped together only because they can be easily understood on the basis of what I have already said of shock. The basic causes of shock following accidents or surgery are the same, and include the "shock-producing factors" of tissue injury, pain, fear, cold, hemorrhage, etc., which I have repeatedly stressed; surgery introduces the added effect of anesthesia. Hemorrhage alone will cause shock if of sufficient severity, simply by the direct production of anoxia; this type responds very favorably to replacement of blood if done before the vicious circle is well established.

Prolonged vomiting or diarrhea, regardless of its cause, will produce shock which is practically identical with traumatic shock except for more pronounced evidences of dehydration. The clinical picture, concentration of the blood, etc., are typical. The diminution of circulating blood volume as a part of the general dehydration has been shown to be the cause of shock in such conditions, and large volumes of saline given intravenously produce great benefit (38).

Diabetic acidosis, if sufficiently protracted, may produce shock; the usual sequence of events is for the shock to develop after a few days of partial or deep coma. Here again, the dehydration is the prime cause

of the circulatory deficiency. In such cases, insulin may bring the blood sugar down to normal and clear the urine of ketone bodies and yet the patient may go on and die of circulatory collapse (28).

The shock-producing effects of injuries to the abdominal organs are well known; military surgeons agreed that circulatory failure developed most rapidly and severely in those whose wounds affected the abdominal viscera, and exposure and manipulation of the intestines is a most effective method of producing experimental shock. Intestinal obstruction, especially if strangulation is present, frequently results in circulatory collapse and death. There appear to be two chief causes for this: first, the loss of fluid by diarrhea and vomiting, and second, the production of a toxic depressor substance in the closed loop of bowel (48). Whipple and his co-workers present strong evidence that such a substance is produced in isolated loops and gives toxic effects when absorbed (p.58).

Visceral ruptures and perforations frequently give rise to shock. This may be an immediate collapse--primary shock--or a gradually developing, typical secondary shock. The degree of shock may be so great that the patient dies within a few hours, before evidence of peritonitis has appeared (48). Cope compared the sudden intense irritation of the peritoneum by gastric or intestinal juices to

the sudden scalding of a skin surface; each produces intense pain sometimes accompanied by immediate syncope or circulatory disturbances of vasomotor origin (81).

Peritonitis frequently gives rise to grave circulatory failure. The familiar peritoneal facies, Fishberg states, is that of shock (28). Cope observed that "In cases of extensive peritonitis secondary shock is seen in its worst form" (81). Stagnation of blood in the dilated capillaries of the enormous peritoneal surfaces, as part of a typical inflammatory process, is probably an important factor here, and extravasation of plasma into the peritoneal cavity may also be significant (28).

Burns will give typical shock, especially if a large area of skin is involved. This is the most important general manifestation of severe burns. If over two-thirds of the body surface is burned, even though superficially, fatal shock usually ensues. The diminution of circulating blood volume is extreme, and the blood shows a degree of concentration scarcely paralleled in any other condition; the viscosity is considerably increased. These factors produce the diminished venous return which characterizes shock.

Blalock and others have demonstrated that local loss of fluid by exudation in the burned area, edema, and blisters amounts to a high percentage of the blood volume.

The plasma is lost almost unchanged through the damaged capillary walls in the burned area (28). Visceral congestion and other evidence, however, indicate that absorption of a toxic substance produces permeability of capillaries in visceral areas, causing an additional important source of fluid loss from the blood (48).

SECTION IX

CONCLUSIONS

1. Although we have learned much concerning the physiologic and pathologic changes which occur in shock, and the phenomenon has lost the veil of mystery which enshrouded it before the War, we still know but little of the causes which initiate these changes.

2. The essential pathology is a loss of tone and an increase in permeability of the capillary walls, caused by injury to the capillaries, and resulting in stagnation of blood in these vessels and transudation of plasma through their walls. The volume of blood "in currency" is thereby decreased, and the blood pressure falls for this reason.

3. Thus shock, in broader terms, develops as a circulatory deficiency of peripheral origin, caused by a decrease in the volume of circulating blood and consequent failure of venous return to the right heart; and resulting

in a supply of oxygen to the tissues which is inadequate for their metabolic requirements.

4. Since tissue anoxemia in itself will cause capillary atony and permeability, it is evident that when the circulation becomes deficient to the point where anoxemia appears, a vicious circle will be established and the shock will become self-perpetuating. This accounts for the well-known tendency for shock, when once established, to become progressively worse until death in spite of any treatment.

5. Many explanations for the initiation of the decrease in blood volume have been advanced. Those which appear to merit our acceptance at the present time are the theories of (a) capillary injury from traumatic toxemia, (b) local loss of fluids to the injured area, and (c) hyperactivity of the sympatho-adrenal system. Any or all of these may cause shock; the relative importance of each seems to vary in different cases.

6. Shock is a condition which results from severe bodily insults of many kinds. There seems to be little point, therefore, in trying to differentiate between surgical shock, traumatic shock, burn shock, etc., other than to indicate the cause, since the end picture in each case is the same.

7. We are not yet in a position to offer any specific therapy for shock, and severe cases still defy treatment.

For this reason, it is important not to wait until shock has become established; we should anticipate its onset and think in terms of prevention.

8. Recent work, however, indicates that potassium is possibly the long-sought toxin of shock, and that adrenal cortical hormone may prove to be an effective treatment. If this work is corroborated, it will be the nearest we have yet come to an understanding of the fundamental nature of shock.

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Note: "Shock Commit. Repts. #25, 26, ans 27" refer to the reports of the special investigation committee on shock and allied conditions, of the Medical Research Committee of Great Britain (p.29). London, H.M.Stationery Office, 1919

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